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The Journal of
Obstetrics and Gynaecology of the British Empire

VOL. LXI, No. 6 NEW SERIES DECEMBER 1954

ATELECTASIS NEONATORUM*

BY

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MR. PRESIDENT, ladies and gentlemen, this is the 16th occasion on which a lecture has been given in memory of William Blair-Bell. In his hard driving career he managed to combine the very active life of a clinician with teaching, which is still vividly remembered, and scientific research on an ambitious and exemplary scale, surely the ideal professional life. Today's subject was not however one of his known activities but were he with us today it would, I am sure, have evoked his dynamic interest and encouragement.

Many distinguished lectures have preceded this one and it is perhaps fitting that the choice of subject today should follow Dr. Walker's convincing discourse last September on foetal anoxia, particularly in regard to postmaturity, for *he* dealt with a variety of asphyxia which occurs *in utero*, and from which the child usually recovers, provided it survives delivery, whereas I would like to deal with asphyxia at the other end of the scale which predominantly concerns the premature infant, not before the moment of its birth, but in the hours or days that follow.

The present low maternal mortality rate is not matched by a comparable decline in foetal loss, and neonatal death rate provides great scope for investigation and improvement since much of it is preventable. Furthermore, although the figures show a drop in foetal mortality due to many other causes, deaths from atelectasis are as common as ever.

In 1936, when Blair-Bell died, deaths under 1 year of age numbered 58·53 per 1,000 related live births, i.e., 35,425 cases. The Registrar General's figures for 1952 show a death rate under 1 year of age of 27·6 per 1,000 live births, i.e., 18,555 cases. In other words, the rate has been more or less halved in that time but if we consider deaths within the first 4 weeks of life the number of cases dying has only fallen by about a third, from 18,254 to 12,331. Of these 12,000 cases approximately half (6,056) were certified as being due to immaturity (3,602) and postnatal asphyxia and atelectasis (2,454). Respiratory difficulties are more frequently associated with prematurity than any other factor and Claireaux (1953), for example, at Queen Charlotte's Hospital has reckoned that 72 per cent of deaths in the premature are so caused. This is more or less everyone's experience.

In the first 15 months of my work at Hammersmith Hospital Dr. Powell and I noted the cause of death in 67 consecutive neonatal deaths (Table I) in all cases whether premature or not. Atelectasis, as usual, heads the list. Intraventricular haemorrhage, of which more presently, is the result of asphyxia; intrapulmonary haemorrhage probably likewise. So that it will be seen that 40 out of the 67 cases (i.e., 59·7 per cent) were due to one variety or another of neonatal asphyxia.

* William Blair-Bell Memorial Lecture, delivered at the Royal College of Obstetricians and Gynaecologists on 21st May, 1954.

TABLE I

Cause of death in 67 consecutive neonatal deaths in 15 months from April, 1952

Asphyxia:	
Atelectasis	18
Intraventricular haemorrhage	12
Intrapulmonary haemorrhage	5
Asphyxia, undetermined	5
	40
Other:	
Haemolytic disease	9
Subdural haemorrhage	6
Congenital abnormalities	6
Pneumonia	5
Peritonitis	1
Total	67

THE ROLE OF PREMATURITY

The surest defence against dying from atelectasis is vaginal delivery at term and, clearly, the prevention of premature labour, which is very much the obstetrician's concern, would be the ideal solution. Baird (1945) has shown that the prematurity rate is more or less inversely proportional to the social status of the patient and a rising standard of living amongst the poorer classes should progressively reduce it. The conservative treatment of placenta praevia, as advocated by Macafee (1945), has already contributed something to the reduction in prematurity and the admission of cases of multiple pregnancy to hospital for enforced rest between the 30th and 34th weeks can do much, as our own experience has shown, to reduce the chances of premature labour in twins. Morison (1952), incidentally, has pointed out that 50 per cent of all twins have a birth weight of less than 2,500 g. The control of pre-eclamptic toxaemia, if this were really feasible, would also reduce prematurity by postponing the eventual need to interrupt the pregnancy. Notwithstanding all this, however, as Eastman has told us in this very room, in the course of a Fairbairn Memorial Lecture in 1951, about half the cases of premature labour remain unexplained and, at the moment, there is no foreseeable likelihood that prematurity will be eradicated from obstetrical practice.

We must therefore turn our attention to a better understanding of the pathology of the premature neonate and seek improved means of dealing with it. Paediatricians and obstetricians have here a common interest and their partnership is paying dividends. The development of premature baby units in hospitals staffed on a generous scale represents an essential advance.

THE FIRST BREATHS

The first few minutes after birth are among the most critical in a baby's whole existence. The baby that drowns in its own liquor and meconium is the victim of unfortunate obstetrics but in the normal, mature case estimates vary as to the rapidity with which the lungs become fully aerated. Clement Smith (1951) considers that full aeration takes several days but Potter (1952) and Claireaux (1954) think that it happens almost at once. Much depends upon the antecedent circumstances and as a general rule the more premature the baby the less readily will the lungs inflate.

Farber and Wilson (1933) have shown that full pulmonary expansion is not accomplished without considerable pressure, sometimes up to 35 cm. of water, but once alveolar expansion has been achieved, much lower pressures are required to maintain it. Thus vigorous respiration is necessary, at least for a variable period initially, to overcome the moist cohesion of the alveolar walls.

The lungs may fail to expand for a variety of reasons. Firstly, an imperfect airway; secondly, because the child may be incapable of making the necessary respiratory efforts because it is either too premature, or is damaged by previous anoxia or the trauma of delivery; thirdly, the lungs may be structurally handicapped by immaturity; fourthly, the thoracic cage may be so soft and collapsible, in the premature infant, that the muscles of respiration fail to get the necessary mechanical purchase, thereby demonstrating the well-known clinical signs of inspiratory recession of the chest wall, as seen in severe degrees of atelectasis. Lastly, the respiratory centre may be too immature to cope, although Potter is inclined to discount this factor and I would agree with her, provided that there is at no time any episode of anoxia, to which this centre is particularly vulnerable in prematurity.

Now the only natural way in which the lungs

can be inflated is by the operation of negative intrathoracic pressures and it would appear to be important to estimate what these pressures are at birth. Fortunately the oesophagus provides a channel through which the changes of pressure within the thorax and mediastinum can be conveniently measured and Dornhorst and Leathart (1952) at St. Thomas's Hospital have successfully used a fine, open-ended polythene catheter, passed half way down the oesophagus. The catheter is filled with water and the meniscus at the end of it is affected by the changes in surrounding pressure. These two workers have employed the method with revealing success in their investigations into bronchitis and emphysema, for example, in adults.

The method seemed obviously applicable to the newborn. The apparatus for measuring such pressures through a fine tube must have a minimal hydraulic admittance to eliminate errors due to viscosity and, for the purpose, we have constructed a modification of the Muller Shillingford photo-electric pressure transducer, and I am indebted to Dr. Shillingford of the Medical Research Council and the Department of Medicine in the Postgraduate Medical School for his help.

After months of preparation I was at last able to obtain a record of this phenomenon (Fig. 1).

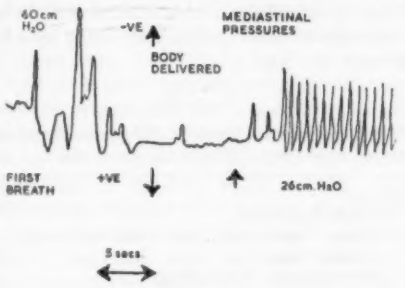

FIG. 1

The mother, a severe diabetic, was delivered by my colleague, Mr. Duncan Murdoch, by Caesarean section under local anaesthesia and I passed a 1 millimetre soft portex tube into the oesophagus as soon as the head was born and before the delivery of the shoulders. The tracing shows that at the second inspiratory attempt, at this stage of the operation, the negative pressure within the thorax drove my recording pen off scale at 60 centimetres of water. This represents no mean effort. Following the delivery of the body a series of very vigorous mediastinal pressures was now exhibited, the child crying lustily. We calibrated our results there and then with the same catheter and the same settings of the apparatus.

I admit that there are pitfalls in calibrating dynamic pressures by means of static methods because the frequency response of the apparatus and the mass inertia of the moving parts may contribute to error; nevertheless, this is as near as we have so far been able to get in making an accurate measurement and I do not think we are far wrong.

The pressures thus demonstrated are an index of respiratory effort. Let us now examine the tidal airs achieved by these pressures as an index of respiratory achievement. Provided the airway is clear and the lungs are normal, achievement that is to say tidal air, should correspond, within certain ranges, to the effort expended, that is to say, the resultant of the intrathoracic pressures evoked by the baby and the better the degree of expansion the higher should be the ratio of tidal air to mediastinal pressure.

For measuring the small tidal airs with which we are concerned in these minute babies, we are using a photo-electric, electronic spirometer in which a beam of light, falling on a photo-electric cell is, more or less, interrupted by the movement of a shutter. A light beam has neither weight nor friction and is therefore suitable for this sort of work. Fig. 2 shows the application of

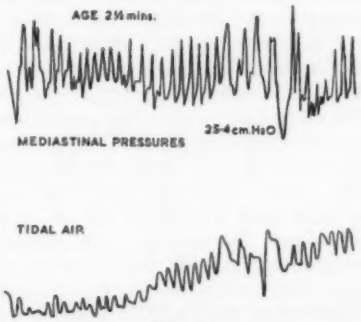

FIG. 2

this principle in the same case as before at the age of 2½ minutes. In Fig. 3 it will be seen that

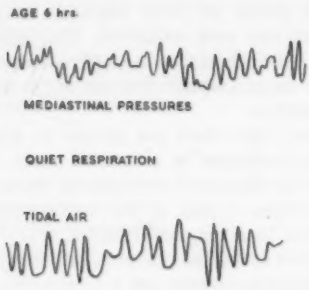

FIG. 3

lower pressures are now achieving a greater degree of ventilation from which I would infer that, in this case, pulmonary expansion was better at 6 hours, although the child was then breathing quietly, than at the time of the previous tracings. An X-ray of the lungs, incidentally taken at the age of 13 minutes, showed good aeration. This method of assessing pulmonary expansion by relating mediastinal pressures to tidal airs strikes me as being full of promise and we are actively pursuing it but it is too early yet to be able to produce a mathematical table, as I originally hoped, of what I would call "coefficients of pulmonary expansion".

Our apparatus, constructed in the Department of Biophysics at the Postgraduate Medical School is sensitive enough to record the mediastinal pressures in an aborted foetus of 26-weeks gestation (Fig. 4). This perhaps unique tracing

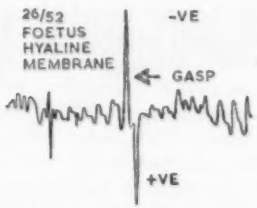

FIG. 4

was obtained in such a baby weighing 1 pound 6 ounces, who subsequently died with atelectasis and it will be seen that, even though the breaths were clinically imperceptible, they were nevertheless being faithfully recorded and the gasp indicated represents a very genuine attempt at coordinated breathing. The tracing demonstrates that the child's respiratory centre was at least functionally competent even at this age.

PATHOLOGY

Some years ago, when I started this work, my attitude was that if a baby was going to die because it breathed inadequately I would produce a machine that would make it breathe but this brought me at once face to face with the pathology that I was trying to treat. Since then my debt to Dr. Claireaux of the Bernhard Baron Research Laboratory has become immense. Nearly all the pathological studies have been made by him and I have personally attended and made notes at practically every necropsy. In the 2 years during which I have been working at Hammersmith I have collected complete dossiers on 133 cases of respiratory difficulty, actual or suspect, in the newborn, the majority being in premature infants. Table II shows the causes of death as found at necropsy. It will be seen that asphyxial deaths account for 45 out of the 57 cases that died and atelectasis in association with hyaline membrane by a long way tops the list.

TABLE II

"Causes" of neonatal death in 133 personally observed cases of respiratory difficulty (57 cases died). 2 years

Asphyxia:	
Hyaline membrane	18
Hyaline membrane and intraventricular haemorrhage	8
Intraventricular haemorrhage	8
Intrapulmonary haemorrhage	2
Pulmonary immaturity	4
Asphyxia, unclassified	5
	45
Other:	
Subdural haemorrhage	3
Congenital abnormalities	3
Pneumonia	5
Kernicterus of prematurity	1
Total	57

Before dealing with hyaline membrane I would like to draw attention to the importance of intraventricular haemorrhage as a cause of death in the premature infant. It differs from subdural haemorrhage in that it is not caused by trauma, as is popularly thought, but is the direct result of asphyxia, whether that asphyxia occurs *in utero* or in the neonatal period. Nearly always the bleeding characteristically occurs from a small ruptured subependymal vessel on the surface of the thalamus. The ventricular system is flooded with blood which tracks through to the subarachnoid space. Subdural haemorrhage, on the other hand, is usually the result of trauma, either through back pressure, induced within the great vein of Galen because of excessive moulding, or due to a frank tear of the tentorium. We have not yet been able to relate the onset of intraventricular haemorrhage to a particular episode of observed asphyxia but it is easy to see that, once it has occurred, the respiratory centre will be still further depressed, thus completing a vicious circle in bringing about the baby's death from asphyxia.

Hyaline Membrane. Atelectasis may be primary or secondary. In the former the lungs never expand at all and the baby does not long survive its birth but, in common with other workers, we have now abundant evidence that the lungs may, for a time, be to some extent aerated and then may secondarily collapse, a condition which Morison has called secondary resorption non-aeration. Most of these babies have at some time during life cried, grunted, maintained a healthy pink colour, shown radiological evidence of at least partial aeration or produced minute volumes which I have been able to measure and yet, at post-mortem examination, the lungs are completely airless and solid. It is clear, therefore, that a continuing and progressive pathological process is at work and histological examination of these lungs will, more often than not, reveal the presence of hyaline membrane. This is not a new disease, in fact Johnson and Meyer fully described it in 1925, but interest in it has steadily grown since that time and it has been recently reviewed by Tran-Dinh De and Anderson (1953) with about 300 references and in 1952 a symposium was devoted to this subject in Philadelphia in which many well-known workers in this field took part.

Hyaline membrane may be defined as a condition in which the alveolar ducts become lined with an eosinophilic membrane which seals off large numbers of alveoli so that either they never expand, or, having expanded undergo secondary resorption, collapse (Fig. 5). The condition is not found in stillborn foetuses, in fact its development depends upon the existence before death of at least 1½ hours respiratory effort and it has been suggested (Claireaux, 1953) that the passage of a current of air through the alveolar ducts is necessary to give it its characteristic distribution. Both its origin and its significance are still under dispute. With regard to the former Claireaux (1953) has suggested that it may be due to the changes occurring in, and conglutination of, squamous cells derived from inhaled liquor amnii and he has been able to reproduce it experimentally from this source in rats. Other views are that it is an exudative phenomenon.

The membrane is known to contain a polysaccharide and might therefore be derived from meconium, which is rich in this substance, or from the above mentioned squames. Intrauterine anoxia, by encouraging deep inspiratory efforts on the part of the foetus, might account for the presence of this material within the lungs but, as Walker has pointed out, and, as we all know, postmature infants are increasingly anoxic, often to the point of foetal distress and the passage of large quantities of meconium, yet, in those that die in the neonatal period, hyaline membrane is an uncommon finding; in fact, I, personally, have not yet encountered it in the postmature. The aspiration of liquor and its constituents *in utero* is therefore not the whole story. Conversely, premature infants are frequently born without any suggestion of intrauterine anoxia and yet they are particularly prone to this condition. My own tentative view is that postnatal pulmonary stasis, which is common in the weak and premature infant, discourages the riddance of deeply inhaled foreign material and favours the development of this membrane by the undisturbed incubation and inspissation of these abnormal constituents; and in support of this view I have observed that

the child whose respiration gets away to a flying start and who breathes vigorously within the first hour or two of life, even though very premature, is unlikely to die of this condition.

Our opinion, in common with that of the majority of observers, is that this membrane is a factor of considerable pathological significance but others, for example, Ranstrom (1953) consider that it has no functional importance in the majority of cases and have noted that atelectasis is not necessarily confined to the areas in which hyaline membrane is histologically demonstrable; but one can no more assess the quantitative effect of hyaline membrane in producing pulmonary insufficiency than one can assess placental insufficiency by examining isolated histological preparations of the placenta.

Another interesting observation is that, if one of twins is going to succumb from atelectasis with hyaline membrane, it is nearly always the second twin, even though the delivery was easy and normal. Claireaux found hyaline membrane to be present in 108 out of 376 cases of neonatal death at Queen Charlotte's Hospital and 80 per cent of these infants were prematurely born and 20 per cent had been delivered by Caesarean section. Potter has also drawn attention to this correlation between abdominal delivery and hyaline membrane, particularly in cases of maternal diabetes. A further interesting fact noted by Gellis, White and Pfeffer (1949) is the increased quantity of fluid which can be aspirated from the stomach after birth, particularly in cases delivered by Caesarean section and in those born to diabetic mothers. We, too, have noticed this connexion. Aspiration of the stomach has become, with us, a routine procedure wherever respiratory function is suspect and in all cases delivered by Caesarean section.

It will be seen that hyaline membrane is no rare pathological curiosity but is as common as it is dangerous. In the 57 deaths in my own series, hyaline membrane was present in no less than 26, in 8 of whom intraventricular haemorrhage was also associated. On the other hand, a further 8 cases of intraventricular haemorrhage were not associated with hyaline membrane.

Diagnosis

Hitherto, the diagnosis of hyaline membrane has only been made by the pathologists after death and we have been at some pains to attempt a diagnosis during life. This is an important matter because, if the condition is reversible, we cannot assess the value of any treatment directed to it without a reasonably certain diagnosis of its existence during life, since, otherwise, the child that recovers does not provide the evidence of histological examination.

The differential diagnosis in neonatal respiratory difficulty is far from easy and is concerned with:

1. Atelectasis, with or without hyaline membrane.
2. Intraventricular haemorrhage.
3. Pneumonia.
4. Spontaneous pneumothorax and interstitial or mediastinal emphysema.
5. Cerebral irritation and raised intracranial pressure.
6. The persisting effects of narcotic drugs given to the mother in labour.
7. Intrapulmonary haemorrhage.
8. Diaphragmatic hernia.
9. Oesophago-tracheal fistula.
10. Cardiovascular congenital anomalies.
11. Pulmonary immaturity.

It is a formidable list. The first three of the above, namely atelectasis, intraventricular haemorrhage and pneumonia, besides being the most common, are also the most easily confused and I well remember the candour of a paediatric colleague when he confessed to me that in the premature infant he had the greatest difficulty in distinguishing between a lesion in the head and one in the thorax. When I mentioned this to another paediatrician he added cynically that I might as well add in the abdominal cavity too! There was a time when I endeared myself to my colleagues by committing them to a diagnosis before death and then rubbing in their mistakes in the post-mortem room, but I gave up this offensive practice when I found my clinical judgment was no better than theirs.

Up to the present it has not mattered so very much whether a baby was breathing indifferently and consequently suffering from asphyxia,

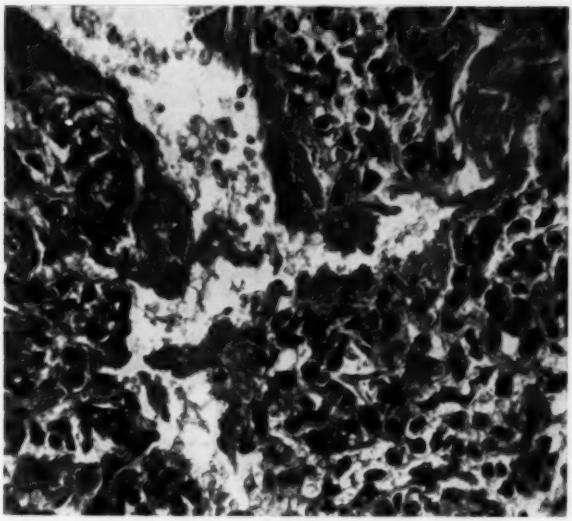

FIG. 5

Hyaline membrane in alveolar duct surrounded by collapsed alveoli. ×360.

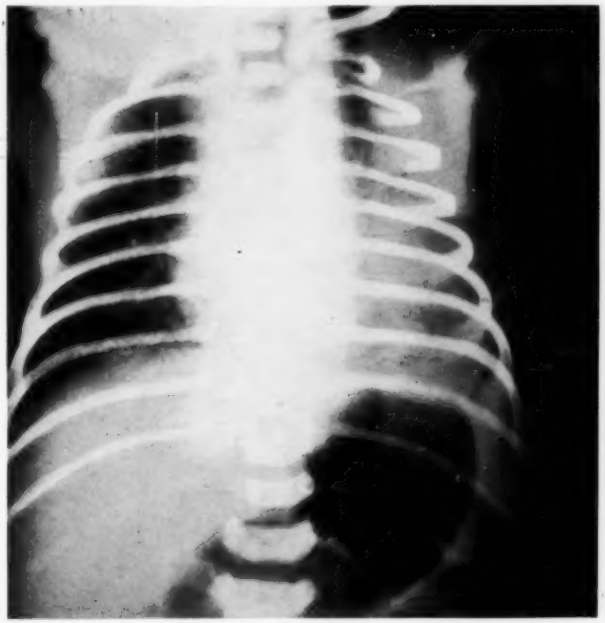

FIG. 6

Hyaline membrane. Fairly early stage. Age 8 hours. Note partial deflation and fine mottling.

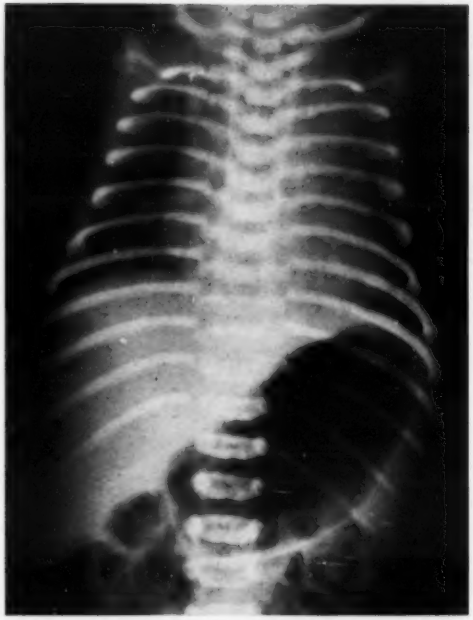

FIG. 7

Hyaline membrane. Another case age 9½ hours. Some coarse mottling. Note outlining of bronchial tree.

FIG. 8

Hyaline membrane. Same case as Fig. 10 at death aged 17½ hours. Total non-aeration and bronchial tree well outlined.

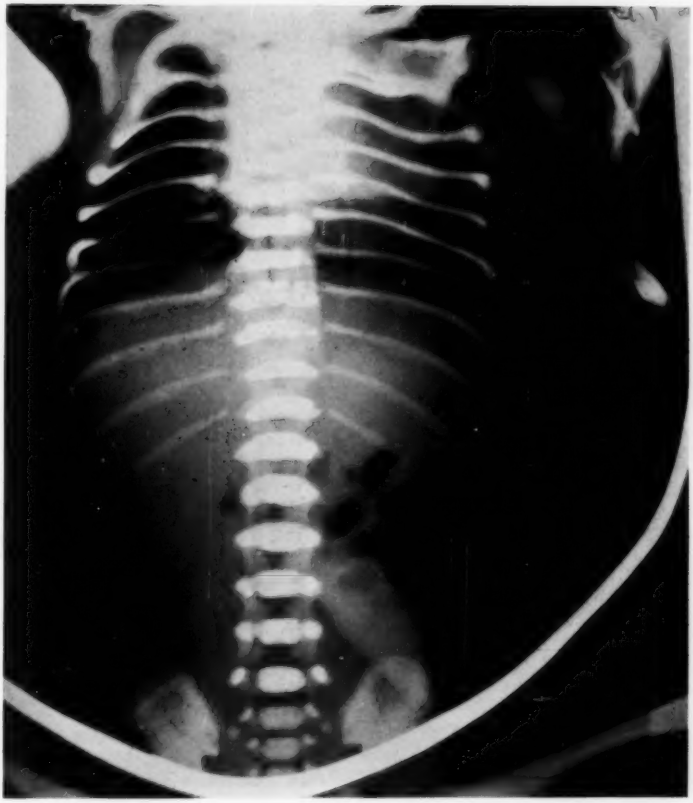

FIG. 9

Case of oesophago-tracheal fistula. Age 40 minutes. Note good pulmonary aeration but minimal gas in intestine which did not increase later.

FIG. 11
Servo Respirator.

I.D.

from central or peripheral causes because the treatment in either case was roughly the same, namely leaving it alone in a warm damp atmosphere rich in oxygen, the ritual use of antibiotics and perhaps a little synthetic vitamin K just for luck. The child is baptized and can thereafter sink or swim and nowhere is an attitude of fatalism more evident than in the management of the very premature child. If anything more specific is to be introduced in the way of active treatment then, obviously, an attempt must be made to arrive at a more specific diagnosis during life both to indicate the treatment and to evaluate its effects.

Asphyxia in the first two days of life very often goes in a series of leaps and bounds, the child looking treacherously pink between attacks of respiratory failure which are usually called blue attacks but would be more aptly described as grey attacks, inasmuch as they are associated with peripheral circulatory failure. There are no pathognomonic symptoms or signs of hyaline membrane. For example the doomed child may cry at the moment of birth and appear pink and vigorous but close inspection half an hour later may reveal the presence of recession of the chest wall, usually in the subcostal region, often sternal and sometimes intercostal and suprasternal. Grunting respirations develop and there may be movement of the alae nasi. In the next few hours the child may either recover a more satisfactory respiratory function or may stop breathing without warning and proceed to go grey. These grey attacks may occur with variable and increasing frequency until, following one of them, life is found to be extinct. Death from hyaline membrane usually occurs between the ages of 3 hours and 3 days, most commonly under the age of 24 hours.

The above clinical description is what I have most frequently observed but is by no means invariable and a similar state of affairs can be demonstrated in pneumonia and in intraventricular haemorrhage. It was obvious therefore that we should invoke the help of radiology and, with the institution of a 24-hour radiographic service at Hammersmith Hospital, we are now able to obtain X-rays at intervals throughout the day or night. We (Donald and Steiner, 1953) have now made a fairly extensive study of the radiological sequence of events in cases of hyaline membrane. Meschan *et al.* (1953) described one such case and indicated the need for a more extensive study. French workers have also interested themselves in the radiological evidences of pulmonary expansion in the newborn. In our own experience we have found that, even in quite pronounced degrees of prematurity, radiological evidence of full expansion is often demonstrable within the first 2 hours.

Now, I have not yet seen a case succumb to atelectasis with hyaline membrane in which a radiological picture of full aeration was previously obtained. This finding alone has been of the greatest value to us in this work as we feel in such a case we can safely pack up our respirators and go to bed. On the other hand, abnormal aeration may be radiologically demonstrated and we have traced three radiological stages in the evolution of atelectasis with hyaline membrane. The conclusion of course is only inferential since the shadows only represent a type of atelectasis of characteristic distribution.

The first stage is one of fine miliary mottling (Fig. 6) which is fairly uniformly distributed throughout the lungs and Steiner reckons that it is probably due to a diffuse alveolar collapse and alveolar consolidation. Caffey, who noted such appearances in 1945, claimed that this was a physiological phenomenon due to structural immaturity but we submit that this is a warning of a pathological state which may progress to the next stage, namely, the appearance of coalescent areas of atelectasis proceeding to lobar or lobular consolidation and collapse (Fig. 7). Finally, in the third stage, the lungs show total non-aeration in which it is hard even to make out the cardiac outline because of the surrounding solid lung (Fig. 8). Nevertheless the bronchial tree, which still contains air, may often be seen outlined, particularly in the mid and lower zones. I have not yet seen a child recover from atelectasis of the third radiological degree although it may continue alive for several hours, but I have to admit that I have never yet tried as hard as I intend to keep such a child going until resolution occurs. It is my secret belief that this will one day be possible.

At the other end of the scale, the child showing

either of the earlier radiological stages may improve or get worse and one cannot tell from an isolated picture which way the cat is going to jump. We therefore take repeated X-rays at intervals of several hours and have noted a fair degree of correlation between the child's clinical state and the radiological appearances. At this point I would like to acknowledge the cheerful and willing cooperation which the radiographers at Hammersmith Hospital have unfailingly shown whatever the hours of night they are summoned.

Quite apart from the help which radiology has brought to bear in indicating the progress, or otherwise, of aeration, the progressive disappearance of these signs in some cases supports my view that hyaline membrane is, at least in its earlier stages, a reversible condition.

A more obvious use of X-rays of course is in indicating other types of intrathoracic pathology, for example, pneumothorax, which is by no means rare and pneumonia which is notoriously difficult to assess.

Another noteworthy point is the rapid spontaneous filling of the gastro-intestinal tract with air which occurs very rapidly after birth and provides a rough index of the child's vigour. The French have referred to this as "aerogastrie" and "aerocolie". A very weak and depressed child fails to gulp down these quantities of air in the course of its respiratory efforts. The phenomenon is of some value as it is generally believed that the child is capable of absorbing oxygen from its intestinal canal. Fig. 9 shows a scanty quantity of intestinal air in a case with nevertheless good pulmonary expansion. This put us wise at an early stage to the presence of an oesophago-tracheal fistula.

Notwithstanding all the above, X-rays provide only a crude index of what is happening and we have devoted some attention to spirometric techniques. Respiration in the very premature infant is often very irregular and the individual breaths may differ widely in size so that, in many ways, an estimate of the minute volume is more indicative of adequate ventilation than the measurement of tidal airs. To meet this need I devised what I have called a "trip spirometer" in which the expired air is collected in a spirometer of known capacity and which is emptied at each filling, the time of filling being recorded by a time marker. In this way a simple bit of arithmetic gives the answer (Fig. 10).

This instrument makes up for its roughness and readiness in its general serviceability and members of our nursing staff have already made over 2,000 calculations of minute volume with it. As a general guide I have found that a minute volume of 100 ml. per pound body weight, as indicated by this instrument, is sufficient to dismiss the likelihood of imminent death from asphyxia and it has been possible to observe the progress or otherwise of a case from hour to hour.

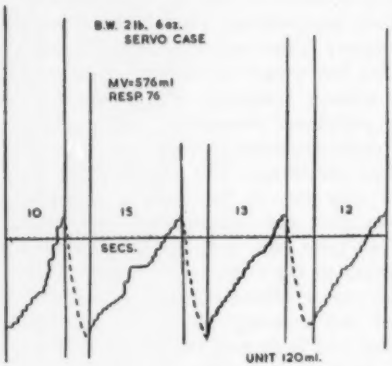

FIG. 10

Lastly, in the assessment of these cases, the relationship between mediastinal pressure and the tidal air achieved looks like providing a further objective indication of the child's state, though we are still in the development stage of this technique. After all, minute volumes are deceptive. A child may, for example, have a low minute volume simply because it is not trying very hard and it may not be trying very hard either because it does not need to, or, because it is incapable of doing so. The simultaneous recording therefore of mediastinal pressures helps to distinguish between the two states.

TREATMENT

We have by no means abandoned the standard methods of treatment in cases of atelectasis in

spite of our developments in respirator techniques. We attach very great importance to the aspiration of mucus and foreign material from the pharynx and also from the stomach from which it is easily regurgitated and which, in the absence of a cough reflex, is likely to be aspirated. We attend to the maintenance of body temperature and to the supply of humidified oxygen. The use of gastric oxygen (Yllpo, 1935) is fairly widely employed by us; but it is one thing to get oxygen into a baby and it is quite another thing to get carbon dioxide out of it and for this an adequate pulmonary ventilation is necessary. Now, you can take a horse to water but you cannot make it drink and likewise you can put a baby in an incubator, rich in oxygen, with no more certainty that it will adequately breathe it and I have therefore been concentrating upon the development of different types of respirator. This work was started at St. Thomas's Hospital many years ago and I continue to be sufficiently impressed with the obvious mechanical difficulties under which a child with atelectasis is labouring to seek a mechanical solution to them. I readily admit the importance of the biochemical processes at work in these cases. The possibilities of anaerobic respiration, too, are interesting but at the moment are more speculative than practical.

First things must come first, and a baby with atelectasis will soon die of exhaustion in trying to overcome its respiratory difficulties. Our objective is therefore to seek ways and means of sharing some of its obvious effort.

I have found that any sort of respirator which worked on a set rhythm was worse than useless and, while still at St. Thomas's, began to experiment with the principle of what the editor of the *Lancet* has aptly termed "augmented respiration". In other words, I have sought to develop a means whereby spontaneous respiratory effort is assisted synchronously with the child's own chosen rhythm, however irregular. In this way the child remains master of the machine which is treating it. The use of pressures out of step with the child's own efforts are either ineffectual, so that the child breathes against the machine, or these indiscriminately timed pressures may irritate and disturb the child and provoke what I call "protest apnoea". Furthermore, if the child is forced to "inspire" at a time when its own diaphragm is not actively contracting, the gases, which it is intended to breathe, may not only encounter a closed glottis but are likely to be diverted down the oesophagus into the stomach. Lastly, the case submitted to this type of arbitrary, artificial respiration is hypothetically capable of being over-ventilated with the production of alkalosis.

My respirators, whether of the emergency, positive pressure type or of the Drinker type, are both operated on the same basic principle whereby the first lifting of the inspiratory valve by the child's attempt at inspiration, deflects a beam of light which operates a photo-electric mechanism (Fig. 11). This triggers the respirator into action so that inspiration is instantly amplified (Donald and Young, 1952; Donald and Lord, 1953). If respirators are to be of any value at all I am certain that, in neonates at least, they must operate on some such principle and Figs. 12, 13, 14, are submitted in vindication. The first (Fig. 12) is a tracing of the mediastinal

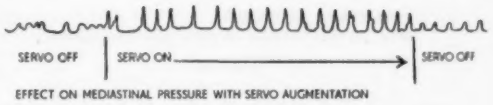

FIG. 12

pressures measured, with the respirator off and on and the improvement in the very forces by which alone expansion of the lungs can naturally occur is obvious. The next (Fig. 13) shows a

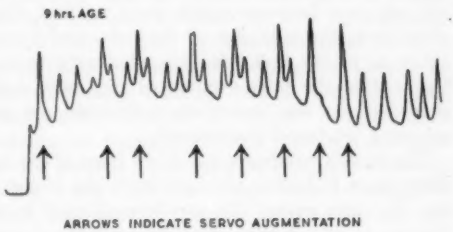

FIG. 13

tracing taken from another case. (Both this case and the one before it are still in our Premature Baby Unit and progressing satisfactorily.) Fig.

14 shows the effect on mediastinal pressures of applying artificial respiration without regard to the child's natural spontaneous efforts. It will be seen that no useful purpose is being served in this instance.

I might here point out that we do not embark upon this elaborate treatment without the need for it being apparent nor have we yet turned down a case for treatment because it appeared too hopeless to try. Our series, therefore, includes a number of previable foetuses. I still do not know how long this treatment should be kept up and the duration would appear to vary between a few hours and possibly 2 days, but in the 57 observed cases of neonatal death already quoted, which include both treated and untreated

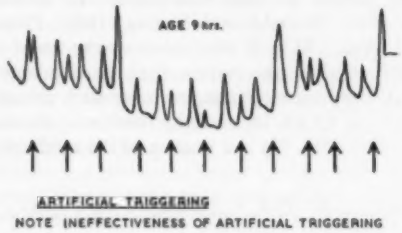

FIG. 14

cases, only 7 died after the first 48 hours so that one's feeling is that if only a child can be safely got over the first 48 hours of life it will have thereafter more than an 80 per cent chance of surviving.

I have to admit that the determining factor in the duration of treatment employed, so far, is an ugly race between which gives up first, the attendants, the machine or the baby and I am ashamed to say that, with my advancing years, I am often the least durable of the three and sheer fatigue has sometimes influenced me in stopping treatment prematurely.

The baby's condition has often been noted to deteriorate following removal from the respirator. To some extent this can be explained by a change in the carbon dioxide content of the atmosphere now breathed. Gunn *et al.* (1952) have drawn attention to the importance of controlling the oxygen content in incubators and Cross and his colleagues (1953) at St. Mary's have shown the effect of carbon dioxide on the respiration of premature infants. Recently, through the generosity of the National Birthday Trust, we have acquired an infra-red carbon dioxide spectrum analyzer and, by determining the carbon dioxide percentage in the respirator and continuing to provide it after the child's transfer to the incubator (when asphyxia is no longer operative), we have been able, in a recent case, to steer the child safely through the next critical 12 hours, between grunting respiration (when too much carbon dioxide was added) and periods of apnoea (when the carbon dioxide was withheld). This promises to be a useful line of after-treatment following removal from the respirator.

RESULTS

It has not yet been possible to make a fair comparison between the treated and untreated cases since we select for treatment those cases which, as a result of our observations and tests, would appear to indicate it. In other words, as far as possible, we select the cases with a bad prognosis and a control series has not so far been a feasible proposition. For one thing cases have not been sufficiently numerous although, in Shakespeare's words, our "appetite is all as hungry as the sea and can digest as much". For another, the selection of untreated controls would involve an identical diagnosis of the clinical condition which, as already pointed out, is not readily to be relied upon and, furthermore, both the birth weight and the period of gestation should be as nearly as possible comparable. Lastly, it would be ethically questionable deliberately to abandon a child to its fate and to withhold a treatment which one believed to be helpful simply in the interests of seeking statistical proof, for what it is worth, of the value of this sort of work.

Table III shows the fate of the untreated cases. Fifty-two survived, of which 1 was previable, and 18 died, of which 2 were previable. The survivors include a number of reasonably fit babies who formed the basis of physiological study.

Table IV shows the results in the cases treated by the principle of augmented respiration. Twenty-three out of 49 viable cases survived and 39 died, of which 13 were previable. In

TABLE III

Untreated 68+(3) cases

Weight (pounds)	Lived	H.M.	I.V.H.	H.M.+I.V.H.	Pneumonia	Other Causes
–2	(1)	(1)	—	—	(1)	1
2–3	5	2	2	1	1	2
3–4	19	3	1	—	—	—
4–5	11	1	—	—	—	—
5–6	1	—	—	—	—	—
6+	16	—	—	—	—	2
Total	52+(1)	6+(1)	3	1	1+(1)	5

Figures in parentheses indicate previable foetuses of less than 28-weeks gestation.
H.M.=Died from atelectasis and hyaline membrane.
I.V.H.=Died from intraventricular haemorrhage.

TABLE IV

Treated 49+(13) cases

Weight (pounds)	Lived	H.M.	I.V.H.	H.M.+I.V.H.	Pneumonia	Other Causes
–2	1	(2)	(2)	(1)	1	(6)
2–3	9	3	(1)	3+(1)	1	2
3–4	6	2	2	1	—	3
4–5	4	2	—	1	1	1
5–6	3	—	—	—	—	—
6+	—	2	—	—	—	1
Total	23	9+(2)	2+(3)	5+(2)	3	7+(6)

Figures in parentheses indicate previable foetuses of less than 28-weeks gestation.
H.M.=Died from atelectasis and hyaline membrane.
I.V.H.=Died from intraventricular haemorrhage.

many of these cases the emergency positive pressure respirator was used only terminally because of recurrent cyanotic attacks, nevertheless these hopeless cases have to be included in the treated group. We can hardly see here "confirmations strong as proof of Holy Writ", nevertheless we do not appear to have done too badly in the weight groups under 3 pounds.

Since the basis for selection of treatment is a bad prognosis, it is surprising that our results are not worse. As it is, the difference in the apparent results between the treated and the untreated cases is less a criticism of the treatment than a vindication of our increasing ability to chose the losers. Our alleged successes, apart from boosting morale which is often very necessary, teach us little or nothing. It is in our failures that real information is to be obtained. I still believe that hyaline membrane is to a large extent a preventable disease, if nipped in the bud early enough, and I remember one memorable Sunday in which 3 premature infants, all weighing between 2 pounds 6 ounces and 2 pounds 12 ounces, arrived one after the other. I was only able to deal with 2 of them, in turn, and the third was reputed to be very fit. Nevertheless the 2 treated cases are progressing well to this day but the untreated case was dead within 9 hours, with hyaline membrane.

Once the lungs have started to solidify with hyaline membrane atelectasis, one is reminded of what it is like trying to stir concrete in a

mixing bucket. It is only a matter of time before the concrete finally sets and no shovel on earth will move it.

No machine can replace good doctoring and, above all, good nursing and I would like to pay tribute to the nursing staff of our premature baby unit, particularly Sister Smith. It may be asked why I, a mere obstetrician, should pursue the fate of these neonates with such remorseless endeavour but obstetricians cannot divest themselves of interest in the fate of the newborn since to give birth to a healthy and surviving child is the whole object of the exercise and without it pregnancy becomes a meaningless ordeal. Anything that we can do to mitigate the hazards of prematurity must, in the end, influence obstetrical technique, for example in reducing the need to postpone termination of pregnancy in the interests of the child (from the point of view of prematurity) in cases of pre-eclamptic toxaemia, ante-partum haemorrhage, chronic nephritis and malignant disease.

The long-term follow-up of cases suffering prolonged asphyxia in the neonatal period is of course not being lost sight of and there would be little point in striving to preserve life which could not thereafter be adequately fulfilled because of damage sustained by the central nervous system. Estimates of the importance of this factor vary. Schreiber (1938), for example, found a history of asphyxia in 70 per cent of 900 spastic or convulsive children. Hellström and Jonsson (1953) consider that anoxia at birth has a less serious prognosis than when occurring after the child has once breathed and started to re-adjust itself to extra-uterine life and this is exactly our problem. I am glad to say that so far none of our surviving cases has yet demonstrated residual disability, nor has retrolental fibroplasia reared its ugly head in any of my series, although looked for by our consultant ophthalmologist.

Our disappointments have been so numerous that we might have given up long ago were it not for our growing realization of the importance of this subject. I have received help in boundless measure which has far exceeded the merits of my research and the encouragement I have had from colleagues, both at Hammersmith and St. Thomas's Hospitals, has made all the difference. The X-ray reproductions are by the Photographic Department of the Postgraduate Medical School and the other illustrations shown are the work of Mr. E. Clark of the Bernhard Baron Research Laboratory, Queen Charlotte's Hospital and I am indebted to them for the speed and skill of their work. I must pay a particular tribute to one of the Institute technicians, Mr. Peter Cowan, who has worked indefatigably and can manage my apparatus far better than I can myself. He has borne patiently with my impatience and the long night hours of toil have not wearied him as they have me. The electronics section of the department of Biophysics of the Postgraduate Medical School, in particular Mr. John Gilbert, have performed feats of electronic wizardry on my behalf. My friends in the Armed Forces have also made notable contributions, in particular Commander Slater of the Fleet Air Arm who has turned up, time and again, in the last 5 years with help. I did not even know what an electro-magnetic relay was when I first met him and he has taught me much. Nor have I lacked funds to pursue this work which even the Inland Revenue Authorities have forborne to tax, funds which, in the form of a Leverhulme Research Scholarship, the Council of this College has been graciously pleased to award me.

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PUERPERAL PANHYPOPITUITARISM

BY

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CASES of Simmonds's disease and diabetes insipidus occurring independently are fairly common, but these two conditions are seldom present simultaneously. Such cases of panhypopituitarism have almost invariably been due to neoplasms. Simmonds's disease occurring alone most commonly follows complications of pregnancy, particularly post-partum haemorrhage, while diabetes insipidus is most commonly associated with neoplastic growth.

Three cases, 2 reported by Spain and Geoghagan (1946) and 1 by Merkel (1914), are known in which lesions of both the anterior and posterior lobes of the pituitary were found at post-mortem. These 3 cases died early in the puerperium, however, before clinical evidence of diabetes insipidus or Simmonds's disease could be detected.

Two cases are on record in which there was definite evidence of both diabetes insipidus and Simmonds's disease developing post-partum. The first (Nassar *et al.*, 1950) was a patient with a twin pregnancy who had a retained placenta associated with severe post-partum haemorrhage. Diabetes insipidus and Simmonds's disease developed and there was still evidence of these conditions 16 months post-partum. The authors adduced evidence to show that the hypofunction of the pituitary gland was due to the large amounts of ergot given. The second case (Storti and Pederzini, 1952) also had a severe post-partum haemorrhage and survived for 2 years. The post-mortem examination, reported by Bracali (1953), showed total necrosis of the hypophysis. Bracali believed that the necrosis occurred because of septic venous thrombosis.

The following is a case which showed evidence of diabetes insipidus and Simmonds's disease developing post-partum.

Case Report. The patient, a secundipara, aged 29 years, was admitted to hospital in a collapsed state following a post-partum haemorrhage. Apart from vomiting in the early months she had been well until one month before delivery when she developed oedema of the hands and feet. There was nothing significant in the previous medical history but it is of interest that, following the birth of her first child in 1947, she was admitted to this hospital in a moderately shocked condition with a post-partum haemorrhage. A transfusion of two pints of plasma was given and the placenta was expressed. Lactation occurred in the puerperium and had to be suppressed with oestrogens as the child had not been admitted to hospital.

The patient received antenatal care from her own doctor and on 12th October, 1952, she delivered a live female child spontaneously in her own home at 1.50 a.m. after a labour lasting 5½ hours. The placenta was expressed by the general practitioner 1¼ hours after the birth of the child. There had been considerable bleeding before and after this manœuvre. Ergometrine, 0·5 mg., had been given intramuscularly shortly after the child was born.

On admission to hospital at 3.35 a.m. on 12th October, her condition was grave. She was restless, her colour was grey, the limbs were cold and grossly oedematous, neither radial pulse was palpable, and the cardiac rate on auscultation was about 160/min. The systolic blood pressure was 60 mm. Hg, and the diastolic

blood pressure was not recordable. On palpation the abdomen was very tender and the fundus uteri firm. There was no bleeding per vaginam.

An intravenous plasma drip was set up at once and 0·5 mg. ergometrine was given intravenously. By 4 a.m. 540 ml. plasma had been given and the blood pressure had risen to 90/60 mm. Hg. Whole blood of the appropriate group was substituted for the plasma and 15 mg. methedrine were given intravenously and 1/6 gr. morphia intramuscularly. A further 15 mg. methedrine were given intravenously 15 minutes later. At 4.30 a.m. the blood pressure was 110/70 mm. Hg and the pulse-rate 138/min. and a second pint of blood was begun. One hour later the patient complained of severe frontal headache and the blood pressure was found to have risen to 175/115 mm. Hg. When the third pint of blood was commenced at 6.30 a.m. the blood pressure had fallen to 120/80 mm. Hg, the pulse-rate remaining at 138/min.

Until this time there had been a satisfactory response to treatment but within 10 minutes there was a sudden, and very marked deterioration. The patient became disorientated, her colour became poor and air hunger was marked, the blood pressure had fallen to 110/70, and, although the pulse-rate had not altered, the quality had deteriorated. Bleeding per vaginam with the passage of clots was apparent. Oxygen was administered and 0·5 mg. ergometrine was given intravenously and 1/6 gr. morphia intramuscularly. By 6.30 a.m. the blood pressure had risen to 150/90 mm. Hg and the pulse-rate had fallen to 124/min.

Intravenous therapy was discontinued at 8 a.m. after a total of 3 pints blood and one pint plasma had been administered. Half an hour later the blood pressure was 150/100 mm. Hg and the pulse-rate 88/min. The restlessness and disorientation were then so extreme that 3·2 c.cm. Bromethol were given per rectum to control the patient. Satisfactory sedation was obtained and the patient slept intermittently until midday when a marked improvement was noticeable; she was rational and calm but had only a hazy memory of events since the birth of her child.

Urine was obtained by catheterization at 11 a.m. on the day of admission and was found to contain 3 parts/1000 albumen. No more urine was obtained for a further 18 hours when 44 ounces were passed spontaneously. The albuminuria persisted until the ninth day of the puerperium.

On the evening of the day after admission her general condition was satisfactory (B.P. 170/110) but vaginal bleeding was excessive. The uterus was explored under general anaesthesia at 11.20 p.m. on 13th October, and a handful of placental tissue removed. The placental site was low on the posterior wall and it was considered that the placenta had been partially accreta. Penicillin, 500,000 units b.d., was begun after the operation but the temperature rose gradually until it reached 102·6 F. on the fifth day of the puerperium; no organisms were cultured from a throat swab or vaginal smears taken at that time. Sulphathiazole 2 g. initially and 1 g. 4-hourly was then given. The temperature had returned to normal levels on the seventh day. Penicillin was given for 10 days and the Sulphathiazole for 4 days. Thrombosis of the superficial calf veins was noted on the seventh day and intravenous heparin therapy was begun but was discontinued after one injection of 5,000 units because of increased vaginal bleeding. The blood pressure on the 3rd, 4th and 5th days of the puerperium was 170/100 mm. Hg, but had fallen to 120/80 by the eighth day and remained at normal levels thereafter. The uterus involuted at the normal rate but lactation was never established, the breasts being soft and painless. No oestrogens were given.

It was noted that the urinary output was high for a few days in the puerperium. Diabetes insipidus was considered as a possible cause of this polyuria but as the urinary output was normal on subsequent days until her discharge on the 19th day (Fig. 1) and the blood NaCl was 595 mg. per cent, the diuresis was considered to be due to the loss of oedema fluid.

Simmonds's disease was considered to be a likely complication in this patient and any evidence of this condition was sought. It was noted that no lactation occurred and the results of an insulin sensitivity (2 units insulin I.V.) performed at this time (29th October) was as follows:

	mg. per cent
Fasting blood glucose ..	75
½ hour	67
1 hour	65
¾ hour	67
1 hour	67
1½ hours	69
1½ hours	77

The 17-ketosteroids measured 3·045 mg./24 hours which is below the lower limit of normality (Selye, 1947).

The absence of lactation and the low level of 17-ketosteroids were indicative of Simmonds's disease but a definite diagnosis could not be made at this time. As she was now feeling well, the patient was discharged from hospital on 30th October and asked to report back in one month.

The patient did not report back until 8th January, 1953, when she complained of polydypsia, polyuria, marked tiredness, loss of libido, and hypersensitivity to cold. She had not

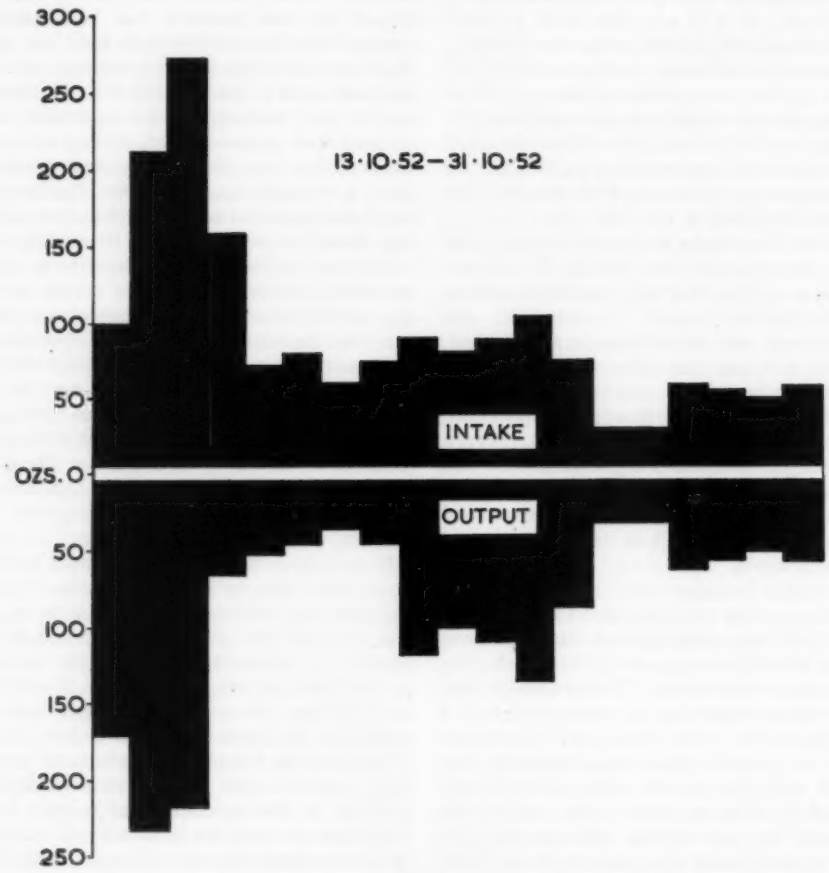

FIG. 1

Fluid balance in puerperium showing initial polyuria followed by normal output of urine.

menstruated. Frontal headaches had persisted since dismissal, and she stated that she was putting on weight. No milk had been secreted and the breasts remained soft and painless. The axillary hair, which had been scanty at the first admission, was totally absent, and the pubic hair was scanty.

She was readmitted to hospital on 12th January. The urinary output and fluid intake are shown in Fig. 2. Several investigations were carried out and the results are shown in Table I.

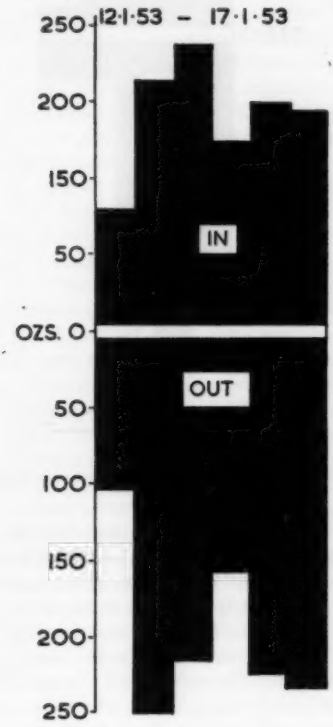

FIG. 2

Fluid balance 3 months after delivery showing polyuria.

By this time there was a marked hypersensitivity to insulin in contrast to the relative insensitivity noted earlier. It is possible that this earlier insensitivity to insulin may have been due to the pre-existing pre-eclamptic toxaemia

TABLE I

URINE

	Chlorides g. per cent	S.G.	17–Ketos.	Pregnanediol
12.1.53	—	—	—	—
13.1.53	0·058	1·000	—	—
14.1.53	0·141	1·002	—	—
15.1.53	—	—	—	—
16.1.53	0·094	—	2·25 mg./ 24 hours	0·55 mg./ 24 hours
17.1.53	0·059	1·002	—	—

BLOOD

	Sodium mg. per cent	Potassium mg. per cent	Urea mg. per cent	NaCl mg. per cent
12.1.53	307	—	31	656
13.1.53	—	—	—	—
14.1.53	—	—	—	—
15.1.53	—	—	—	—
16.1.53	315	—	21	613
17.1.53	—	18·66	—	—

14.1.53 INSULIN SENSITIVITY (2 units insulin I.V.)

	F	1	2	3	4	5	6
Sugar mg. per cent	76	33	35·5	42	54	59	74

15.1.53 GLUCOSE TOLERANCE

	F	1	2	3	4	5
Sugar mg. per cent	86	127	106	106	65	61

All specimens of urine negative for sugar.

(Govan *et al.*, 1951). As would be expected the hypersensitivity to insulin was accompanied by an increased tolerance to glucose.

In view of the clinical findings, the low 17-ketosteroid level and the hypersensitivity to insulin a diagnosis of Simmonds's disease was made. In addition, the marked polyuria and polydypsia, the hyperchloraemia, the low urinary chlorides, and the low specific gravity of the urine pointed to a diagnosis of diabetes insipidus. This condition must, however, be differentiated from hysterical polydypsia. In order to do this the patient was asked to refrain from taking fluids for as long as possible. This she was able to do for 5 hours. The results are shown in Table II.

In contradistinction to hysterical polydypsia the specific gravity of the urine did not increase. The contrast between the day and night urinary

TABLE II

Time	Volume	Specific Gravity
	ml.	
4 p.m.—5 p.m.	800	1·001
5 p.m.—6 p.m.	340	1·001
6 p.m.—7 p.m.	280	1·003
7 p.m.—9 p.m.	440	1·003

output is shown in Table III, and it is seen that there is only a slight nocturnal concentration of urine.

TABLE III

Time	Volume	Specific Gravity	Chloride
	ml.		mg. per cent
12 m.n. — 3 a.m. ..	980	1,001	0·082
3 a.m. — 6 a.m. ..	340	1,003	0·117
6 a.m. — 9 a.m. ..	960	1,001	0·117
9 a.m. —12 noon ..	1,500	1,001	0·096
12 noon— 3 p.m. ..	1,260	1,001	0·070

The results of B.M.R. readings were equivocal but this is a common finding in cases of Simmonds's disease. Repeated radiographs of the sella turcica have been negative. Thorn's test was performed on 28th January, 1953 (25 mg. A.C.T.H.) and the eosinophil count fell from 44/c.cm. to 22/c.mm. The 17-ketosteroids now measured 6·96 mg. per cent and the pregnanediol was 0·6 mg. per cent. The weight at this time had not altered, being 165 pounds.

As a final test in the diagnosis of diabetes insipidus, 1 c.cm. pitressin tannate in oil was injected intramuscularly and the striking effect on the urinary output is shown in Fig. 3.

The diabetes insipidus has been controlled with regular injections of pitressin tannate and at the time of writing (18 months after delivery) the patient is alive and well. She menstruated on one occasion, following injections of anterior pituitary hormones in March, 1953. There has been recent evidence of recovery from the Simmonds's disease in that menstruation occurred spontaneously without hormone injections in July and October, 1953 and January, 1954. In addition the scalp hair has begun to grow again. Despite this the patient has observed that she had to cut her toe-nails on only one occasion (June, 1953) but has never required to cut her finger-nails since the birth of her child. It is of interest to note that aspirin nullifies the effect of the pitressin tannate. In January, 1954 the 17-ketosteroids measured 9·5 mg./diem and the corticoids 6·6 mg./diem.

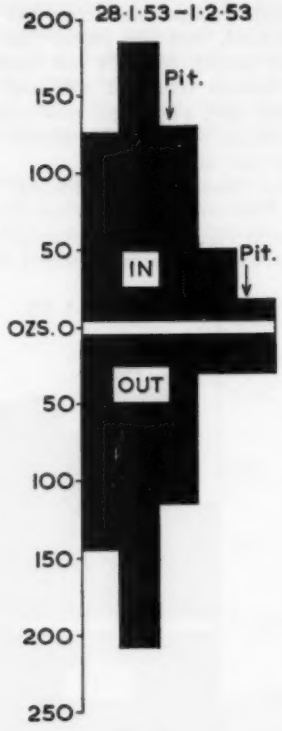

FIG. 3
Effect of pitressin tannate on urinary output.

DISCUSSION

From the clinical and laboratory findings there seems little doubt that this patient has a combination of Simmonds's disease and diabetes insipidus, although there appears to be a tendency towards spontaneous cure of the Simmonds's disease. The lesion in this case may be in the pituitary gland itself or in the adjacent

hypothalamus. Certain evidence suggests, however, that lesions have occurred in the anterior and posterior lobes of the pituitary gland. The diabetes insipidus is pronounced whereas the Simmonds's disease is not of severe degree and shows a tendency to spontaneous recovery which indicates that the lesion in the posterior lobe is of greater severity than that in the anterior lobe. Were the lesion in the hypothalamus one would tend to expect an equal degree of anterior and posterior lobe hypofunction. Furthermore, Camus and Roussy (1920) state that lesions in the hypothalamus cannot be controlled by injections of posterior lobe extracts. The spontaneous tendency to recovery from Simmonds's disease without any alteration in the degree of diabetes insipidus suggests that individual lesions occurred in the anterior and posterior lobes. The 4 comparable cases which have been reported (Merkel, 1914; Spain and Geoghagan, 1946; Storti and Pederzini, 1953) were found at post-mortem to have degenerative lesions in the anterior and posterior lobes of the pituitary gland.

It has been shown in animal experiments (Selye, 1947) that when both the anterior and posterior lobes of the pituitary gland are removed polyuria does not occur. This is presumed to be due to the removal of the diuretic effect of the anterior lobe. As a marked polyuria occurred in our case in spite of anterior lobe dysfunction it must be concluded that the lesion has been focal and selective and the area of the anterior lobe concerned with the production of the diuretic factor has not been involved in the degenerative process. All the comparable cases which have been reported have been associated with profound shock not in all cases due to haemorrhage (Merkel, 1914; Spain and Geoghagan, 1946; Nassar *et al.*, 1950; Storti and Pederzini, 1952). Nassar's suggestion that the lesion may be due to ergot does not appear to be true as the present case did not receive excessive amounts of ergometrine. Bracali's suggestion that the lesion was due to septic venous thrombosis may well be true as in all cases there was a history of sepsis.

The present case also exhibited profound shock and this appears to play an essential part in the production of the combined lesions. The extreme rarity of the condition probably lies in the fact that, where such profound shock occurs, the patient succumbs before sufficient time elapses for the development of the lesions.

Summary

A case of combined Simmonds's disease and diabetes insipidus following profound shock due to post-partum haemorrhage in a patient who had evidence of pre-eclamptic toxaemia is reported.

Evidence to support the diagnosis of the two conditions is presented and further, that the lesions are in the anterior and posterior lobes of the pituitary gland.

The lesion in the anterior lobe appears to be of fairly mild degree and is not involving the area concerned with the production of the diuretic factor. Spontaneous recovery appears to be occurring in the anterior lobe as the signs of Simmonds's disease are disappearing.

Only 5 cases of anterior and posterior pituitary necrosis following pregnancy have been reported in the literature and 3 of these died early in the puerperium. The other 2 cases developed diabetes insipidus and Simmonds's disease and one of these showed necrosis of the anterior and posterior lobes of the pituitary gland at post-mortem several months later.

It is suggested that the combined lesions of the pituitary gland are rare because patients succumb from profound shock too early for the lesions to develop.

We wish to acknowledge our indebtedness to Professor Lennie for permission to publish this case and to Dr. A. D. T. Govan, Director of Research, for his help in carrying out the investigations.

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SOME FORM VARIATIONS IN ENDOMETRIAL TUBULES

BY

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INTRODUCTION

THERE have been many descriptions of the normal histology of the endometrial tubule since Hitschmann and Adler published their classical account in 1908. Details have been added by numerous authors and certain features of the cyclical changes which take place have been related to advances in other fields, notably endocrinology (O'Leary, 1929, 1931; Sturgis and Meigs, 1936; Rock and Bartlett, 1937 and others). In all these accounts, however, the emphasis has been, as would be expected, on the changes taking place in the tubules in the various stages of the menstrual cycle; little attention has been paid to form variation in individual tubules in the same specimen of endometrium. The tubule is described as being essentially a simple tube in the early stages of the menstrual cycle which becomes more and more tortuous as the cycle advances and which, usually at about the middle of the cycle, begins to show evidence of secretory activity. There is little to be found in these published accounts of any variation from this basic pattern. It is in a sense surprising that more attention has not been paid to the normal in the endometrium for it affords a very good example of the truism that knowledge of the normal is an essential prerequisite to understanding of the pathological. Failure to appreciate the variations of the normal in the endometrium has led in the past to certain patterns now known to be normal being included among those due to disease.

The most frequently occurring reference to any variation from the basic type of structure of the endometrial tubule is the statement that branching does sometimes occur, especially in the deeper parts (Eden and Lockyer, 1935). In two standard works only has any reference been found to the very common appearance illustrated in Fig. 1 where some organized structure is found to lie within the lumen of the tubule. This appearance is illustrated by Eden and Lockyer (1935) who say: "More common than branching is invagination of a portion of the gland wall into the lumen so that on section a small ring appears within a larger one." In one other work (Teacher, 1935), there is an illustration of a rather more complicated protrusion which is labelled: "Section through tortuous glands giving the appearance of invagination." Although it is not quite clear what is meant here the impression is that the author believes that this appearance is due simply to tortuosity and that the appearance of invagination is an artefact.

All pathologists will be familiar with the appearance shown in Fig. 1. The question of whether or not this type of appearance is to be accounted for by artefact, whether due to processing in the laboratory, to trauma at the time of operation or to tortuosity of the tubule, is of primary importance. Browne (1952) concluded that the appearances could be produced by artefact but his study was based on simple sections only and no serial sections were studied. His opinion was that the appearances might be caused by a vacuum effect due to withdrawal of a dilator before curettage. Examination of the proximal ends of the affected tubules, as seen in serial sections, seems to make this view untenable: there is no withdrawal of the tubule as a whole from the surrounding stroma nor are there any breaks in the continuity of the lining epithelium. There is no doubt that section through a suitably convoluted tubule can produce the appearance of an intratubular protrusion. This may occur when section is made through a sharp bend in a tubule but in such a case the appearance will be of a solid mass of

PLATE 1

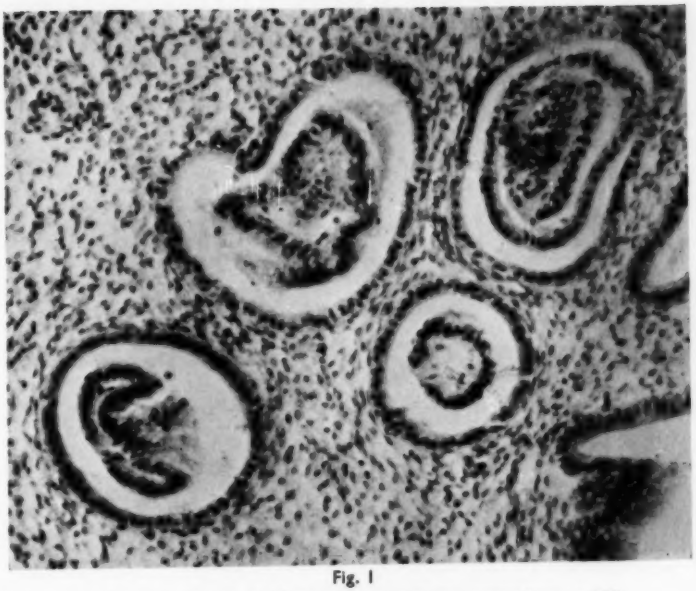

Fig. 1

A typical low power field showing intratubular protrusions. ×175.

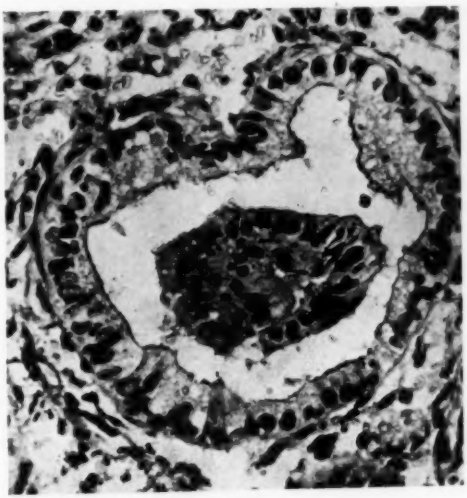

Fig. 2

Intratubular protrusion of non-secretory structure in a tubule which shows secretory activity. ×375.

F.H., L.M.G. 1744

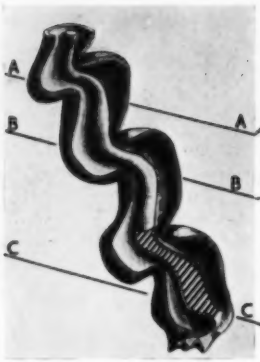

Fig. 3
Drawing of reconstruction of Tubule I.

Fig. 4

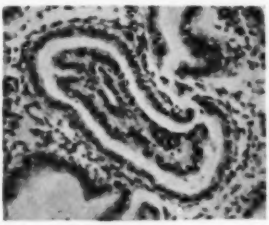

Fig. 5

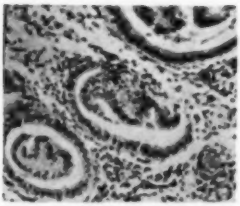

Fig. 6

Figs. 4, 5 and 6
Photomicrographs showing the appearances at levels approximating to AA, BB, and CC. ×100.

F.H., L.M.G.

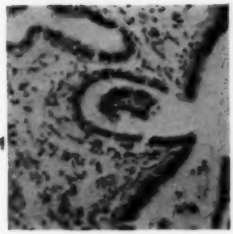

Fig. 8

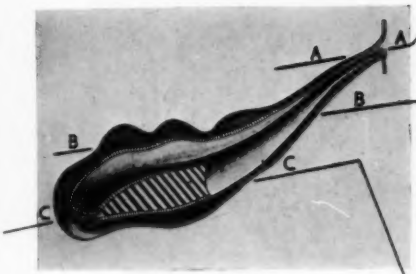

Fig. 7

Drawing of reconstruction of Tubule II.

Fig. 9

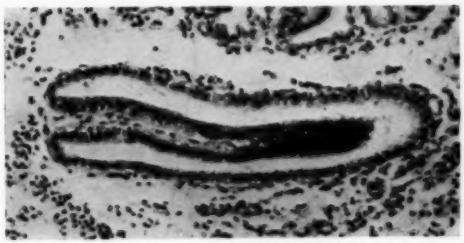

Fig. 10

Figs. 8, 9 and 10

Photomicrographs showing the appearances at levels approximating to AA, BB and CC. $\times 100$.

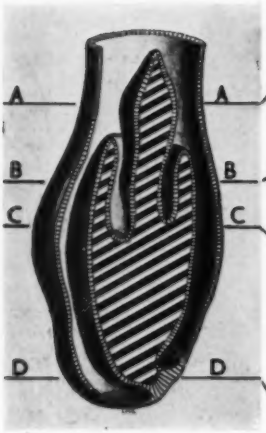

Fig. 11
Drawing of reconstruction of Tubule III.

Figs. 12, 13, 14 and 15
Photomicrographs showing the appearances at levels corresponding to AA, BB, CC and DD. ×240.

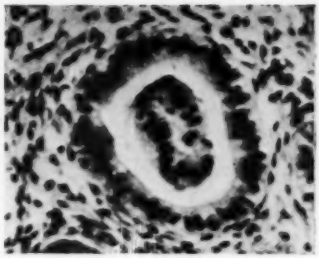

Fig. 12

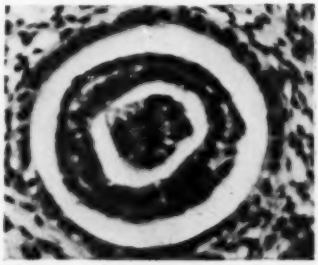

Fig. 13

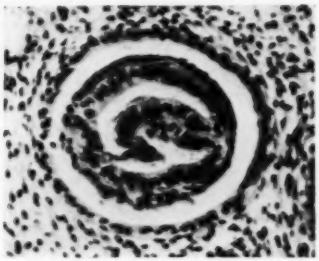

Fig. 14

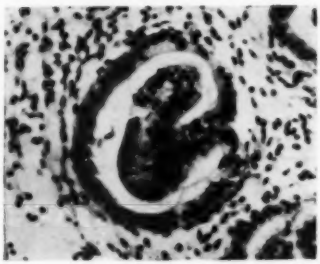

Fig. 15

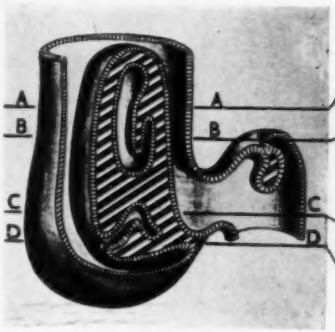

Fig. 16
Drawing of reconstruction of Tubule IV.

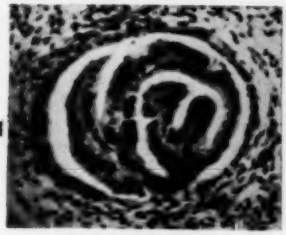

Fig. 17

Fig. 18

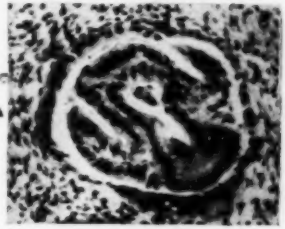

Fig. 19

Fig. 20

Figs. 17, 18, 19 and 20
Photomicrographs showing the appearances at levels approximating to AA, BB, CC and DD. ×200.

Fig. 21
Drawing of reconstruction of Tubule V.

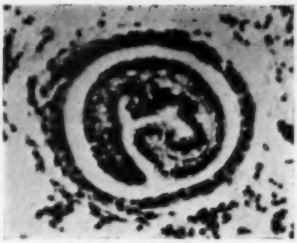

Fig. 22

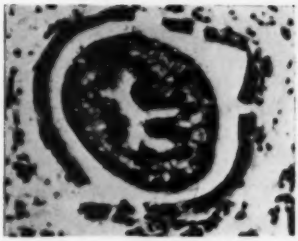

Fig. 23

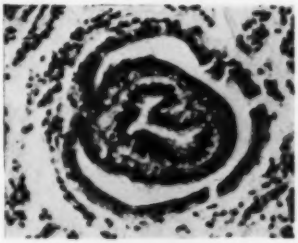

Fig. 24

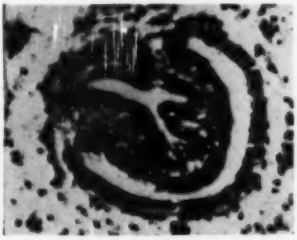

Fig. 25

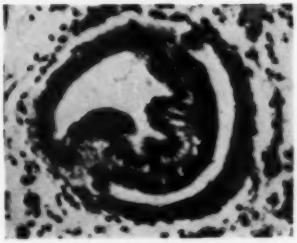

Fig. 26

Figs. 22, 23, 24, 25 and 26
Photomicrographs showing the appearances at levels approximating to AA, BB, CC, DD and EE. ×200.

F.H., L.M.G.

cells within the lumen and not of one tubule within another as is sometimes seen. The true state of affairs in such an artefact will be made plain if a few serial sections are examined when it will be found that the appearance never persists over fifty or more sections as it does when a genuine intratubal protrusion is examined. Where the effect is due to artefact it will be found that it is present over a very much smaller number of sections. There appear to be two considerations which make it likely that the appearance of these intratubular protrusions is genuine and not due to artefact. In the first place the appearance may persist over a hundred or more continuous serial sections and the point of origin of the protrusion from the wall of the tubule can be clearly demonstrated. Secondly it is observed that the protrusion and the tubule within which it lies often differ strikingly as far as secretory activity is concerned. Often it is found that where the epithelium of the parent tubule is in the secretory phase the epithelium of the protrusion itself is non-secretory. Examples of secretory change in the epithelium of a protrusion have been seen but the more usual appearance is non-secretory. The contrast between the two types of epithelium can be striking and is clearly shown in Fig. 2. Against the suggestion of production by artefact due to trauma associated with curettage is the fact that these protrusions are found in hysterectomy specimens.

It is the purpose of this communication to report on the incidence of these intratubular protrusions and to give an account of some of the variations of structure within them.

Material and Methods

The material consists of 225 specimens of endometrial curettings received consecutively in the laboratory. The material has not been selected in any way and comes from patients suffering from a wide variety of gynaecological disorders. Many of the endometria were normal and came from patients whose only complaint was of failure to conceive. The frequency of the condition has been assessed by determining the proportion of cases which showed intratubular protrusions.

In selected cases, where the appearance on simple section indicated that protrusions were present or that some other unusual feature might be found, serial sections 5μ thick were prepared. Usually between one and two hundred sections were prepared from each case. In such series the fate of the intratubular protrusion could be studied over a considerable length of tubule and in many cases it was possible to cover the whole length of the protrusion from its origin to its termination. More detailed studies were made of numerous tubules showing the effect and in 5 of these the appearances were believed to merit description. In these cases camera lucida drawings were made of every section in the series and these were then traced on to plasticine of uniform thickness. Copies of the sections of the tubules under consideration were then cut out in plasticine and by assembling them one above another a reconstruction of the tubule and its protrusion was obtained. When a correction had been introduced, relating the thickness of the section to the thickness of the plasticine replica, it was possible to make drawings and also wax models which were very approximately to scale. It is by such methods that the drawings presented in this paper have been obtained.

Results

(1) *The Incidence of Intratubal Protrusions*

The 225 consecutive curettings were examined for the presence of this phenomenon. It was found to be present in 85 cases, i.e., 38 per cent. Browne (1952) states the overall incidence of the phenomenon as 78 per cent of all curettings in a small series of 50 cases and compares this with an incidence of 14 per cent in sections obtained from hysterectomy specimens. He cites these figures in support of his contention that the effect may owe something to artefact in so far as curettings are concerned. It is believed, however, that the much higher average age of patients undergoing hysterectomy as compared with the average age of those having a simple curettage will probably account for the difference in incidence. The effect of hormonic stimulation in the two classes of patients is likely to be quite different. No attempt has been made to assess the degree to which the tubules in any one

endometrium are affected. In any section a given tubule may be cut through once or several times and this may give an unduly high impression of the number of tubules which contain protrusions. On the other hand, sections through one tubule containing a protrusion may give the effect that several tubules have been cut across, only one of which contains the protrusion and thus the incidence of protrusions may be recorded as lower than it actually is. The appearances when such a tubule is cut are shown in Fig. 9.

Of the cases studied, 27 were regarded as showing frankly pathological features and the remainder were considered normal. The phenomenon of intratubular protrusions was found to be present in 2 out of the 27 abnormal cases and in 83 out of the 198 normal cases. The frequency of the condition, especially in endometria which were normal in all other respects, leads to the conclusion that these protrusions are without pathological significance.

The incidence of these protrusions in relation to the ages of the patients has also been considered. If patients are placed into 4 groups, 0–30, 31–40, 41–50 and those over 50 years old it is seen that the proportion of endometria showing the effect diminishes with age. (See Table I and Charts I and II.)

TABLE I

Age (years)	No. of Cases	No. Positive	Percentage Positive
Less than 30	77	38	49
31–40	61	26	43
41–50	45	15	33
Over 50	17	2	12

If the incidence in patients below and above the age of 40 is considered, the results are as shown in Table II.

TABLE II

Age (years)	No. of Cases	No. Positive	Percentage Positive
Less than 40	138	64	46
Over 40	62	17	27

Difference in Proportion: 19 per cent.
Standard Error of Difference in Proportion: 7 per cent.

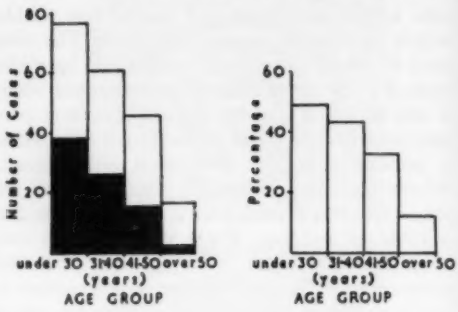

CHART I CHART II

Chart I shows (solid areas) the number of cases showing the effect and the total number of cases studied.
Chart II shows the percentage of cases showing the effect in relation to the age groups given.

(2) *Some Form Variations Observed*

The detailed structure of the protrusions which were observed has been seen to show numerous variations. From the cases which were followed 5 tubules were chosen for illustration as showing different structural variations. These cases are illustrated in Figs. 3–26. In each case a drawing of the reconstruction of the tubule and its protrusion is shown, and also several sections at different levels have been photographed in each case to show some of the important features of these protrusions.

Considerable variation has been found in the degree of secretory activity shown by the protrusions as compared with that of the tubules within which they lie. In all cases where the tubule as a whole was in the proliferative stage the appearance of the protrusion was in accord. In some cases where the tubules showed early secretory activity as manifested by the presence of subnuclear vacuolation the protrusions also appeared to be in the same stage. In other cases they did not show these changes. Wide variation was found in those endometria which were, as a whole, in the fully developed secretory stage. Rarely the protrusion itself showed full secretory activity. More commonly it was seen to be non-secretory in structure as illustrated in Fig. 2. In such cases the tubule containing the protrusion might itself show secretory activity as in Fig. 2, or in some instances, although the tubules

as a whole were secretory, the particular tubules containing protrusions were found to be of non-secretory pattern.

Plate 2. This reconstruction illustrates the state of affairs in a tubule, simple transverse section of which may show the appearance illustrated in Figs. 4 and 5. This is the commonest type of manifestation and simple section shows two layers of epithelium, an outer layer which is the epithelial lining of the tubule proper and an inner layer which covers a solid central core. Reconstruction shows a simple polypoid column arising from the lower extremity of a rather tortuous tubule. Figure 6 shows the appearance at the place of attachment of the protrusion to the main tubule. At this point the two layers of epithelium are continuous.

The apparent cleft in the protrusion seen in Fig. 4 is in reality a simple grooving of the protrusion. Such appearances are common and their true nature can be established only by the examination of serial sections.

Plate 3. This shows another simple intratubular protrusion which in this case has been sectioned in an almost horizontal plane. In this case the protrusion can be traced right up to the orifice of the tubule at the surface of the endometrium. The section at the level indicated by BB in Fig. 7 shows how the appearance of more than one tubule may be produced in a simple section through a tubule at a place where there are localized pouches in its wall. This illustrates how an erroneous idea of the number of tubules containing protrusions may be gained if single sections only are examined.

Plate 4. This diagram (Fig. 11) shows the state of affairs in a tubule which may, in simple section, present the appearance of three concentric structures as shown in Fig. 13. The outer ring is the tubule proper, the next structure, also a ring, is covered by epithelium on both aspects and the innermost structure is a solid core covered by a layer of epithelium. In this case reconstruction shows the protrusion to be rather more complicated than those previously described. It begins at the base of the tubule and continues as a simple polypoid structure for about half its length. Its attachment to the tubular wall is shown in Fig. 15. The appearance at the upper end is as if the subterminal portion of the protrusion had become invaginated into the main body of the structure or as if the protrusion had developed a tubule within itself into which a new protrusion had arisen and grown up beyond the limits of the original protrusion. The base of attachment of this secondary protrusion is clearly shown in Fig. 14. Fig. 12, a section taken towards the tip of the protrusion, shows that the three concentric structures have now been reduced to two as is explained in the diagram.

Plate 5. Figs. 17 to 20 show a more complicated arrangement where the protrusion itself shows the presence of clefts and spaces within its substance. The diagram, Fig. 17, shows how these appearances are produced. It is seen that a closed cavity has developed within the protrusion and Figs. 17 and 18 show this to be lined by epithelium. Within this cavity another protrusion had developed which this time points downwards. This is included in Fig. 18 and its attachment is shown in Fig. 17.

The basal portion of the main protrusion shows a cleft, opening at the surface and blind at the other end which is lined by epithelium. The sections and the diagram show how the more complex appearances sometimes seen in a simple transverse section may arise.

Plate 6. This specimen illustrates the mode of production of the type of appearance seen in Fig. 23. Here there is an outer tubule and within it is a structure covered by epithelium and with a cavity in it which is also lined by epithelium. This appearance is seen to arise by the invagination of one tubule into another or into itself. The material available for section did not permit of an accurate appraisal of the situation below the level EE in Fig. 21. Figs. 26, 25 and 24 show the gradual enclosure of one tubule by the other and in Fig. 23 the process is seen to be complete. In Fig. 23, therefore, the outermost layer of epithelium and the layer next to it are both derived from the outer tubule whilst the innermost layer of epithelium is the lining epithelium of the invaginating tubule. A further point in this specimen is that the epithelial layers of the two tubules have fused at the apex of the invaginating tubule and a pore has been formed so that the lumina of the two tubules are in communication. This pore is clearly shown in Fig. 22.

Discussion

Intratubular protrusions of several different types occurring in human endometrium have been described. It is not suggested that all the possible variants have been observed and indeed it seems likely that a larger series of cases would show other types of protrusion. The present paper describes simple polypoidal protrusions, protrusions containing clefts, protrusions containing tubules within their substance, protrusions containing tubules within them which themselves contain protrusions, and one intratubular protrusion formed by the invagination of one tubule into another or into itself.

The age incidence of the phenomenon has been described and it is seen that the incidence decreases with age. In the series studied the difference in incidence in women under and over the age of 40 is statistically significant. This finding will probably account for the fact mentioned by Browne (1952), with which our experience agrees, namely that the phenomenon is commoner in biopsy specimens than in sections prepared from uteri removed by operation. The majority of women undergoing hysterectomy are more than 40 years old; the majority of women having a simple dilatation and curettage are less than 40. The mechanism of production of these protrusions and the explanation of the fact that a given tubule and its protrusion often show a difference in secretory activity remain in doubt. It would appear likely than an explanation is to be sought in the different blood supplies received by the basalis and the endometrium proper. Daron (1932) showed that the endometrium as a whole receives its blood supply by two different types of vessels. The first type are small and do not extend beyond the basalis and the second type are the spiral arterioles which enter the endometrium as continuations of the radial arteries of the myometrium and which proceed to the surface as tight coils. Paine (personal communication) suggests that some imbalance between the blood supply from the one type of artery and that from the other might result in the formation of these protrusions. Here it is important to note that in almost all the tubules studied the protrusion has arisen at or near the proximal end of the tubule where its blood supply would be that of the basalis. If an attempt is made to explain the failure of secretory activity often seen in the protrusions by a consideration of vascular arrangements it appears at first sight that this can only be done by introducing an apparent contradiction about the roles of the basal arterioles and the spiral vessels. It would seem that to account for the formation of the protrusions one must propose a relatively excessive basal blood supply and a relatively diminished spiral supply, and to account for secretory discrepancies one would suggest that the protrusion, receiving its only supply from the basalis, is relatively ill-nourished as compared with the tubule proper which receives capillaries from the spiral arterioles. This apparent contradiction would be resolved if it could be shown that in cases where this phenomenon occurs the regeneration of the spiral arterioles after menstruation is slow and hence a preponderance of basal influence during the proliferative phase, but that later it becomes adequate and by the secretory phase is able to supply the tubule more efficiently than the basal artery can supply the protrusion.

The likeness of those protrusions to small polyps raises the possibility of their being produced by a similar mechanism. Their failure, in some instances, to show secretory activity suggests a possible analogy with what Novak (1947) calls areas of "unripe" endometrium. He pointed out that it is not uncommon to find areas of endometrium which are of non-secretory pattern in a section which shows, as a whole, secretory activity. He stated that in a typical endometrial polyp it is sometimes possible to trace a layer of non-functional tissue through the polyp itself, as it projects above the surface, through the functional layer of the endometrium and into the non-functional basalis. These protrusions, too, are sometimes non-secretory in a secretory tubule and it may possibly be that there is some underlying factor common to the formation of these protrusions and typical endometrial polyps; that the former may possibly be considered to be "micro-polyps".

It was at first thought that these protrusions might be manifestations of hyperplasia; the general effect of exuberant growth displayed by them suggests that this might be so. The evi-

dence, however, is against this. The incidence is high in curettings which are otherwise normal, higher in fact than in cases which show evidence of hyperplasia. Indeed in cases showing the phenomenon of hyperplasia at its most distinct, the "Swiss Cheese" endometrium of Novak, the effect has so far not been seen.

The formation of clefts and tubular spaces within the protrusions raises several points. These clefts, lined by epithelium similar to that of the protrusion itself, may arise as downgrowths from the surface, dipping into the body of the protrusion itself and in such a case they may or may not maintain an opening at the surface. They might also arise as nests of epithelium which are buried in the protrusion at its origin, and which at a later stage develop a tubular structure. If such is the case it would appear that these clefts or tubules which open at the surface do so by a process of fusion of two layers of epithelium. That such a fusion can occur is implicit in the explanation offered of the appearances shown in Plate 6.

Summary

The occurrence of certain form variations, associated with the presence of intratubular protrusions, in endometrial tubules is described. The incidence of this condition is assessed. It is considered that these variations have no pathological significance. Certain tubules showing these protrusions have been studied by serial sections; plasticine models of the structures have been made and drawings prepared from them have been described. The structure of 5 tubules showing the presence of intratubular protrusions is described in detail. Possible modes of origin of the phenomenon are discussed.

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PLACENTAL TRANSMISSION OF ANTIBIOTICS

BY

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MANY investigations have made it clear that the child may die from pneumonia before birth, or succumb soon after delivery with advanced pulmonary disease. How pneumonia occurred before birth remained a mystery until it was demonstrated that breathing is a normal physiological process of the foetus *in utero*. Barcroft (1935) had demonstrated this phenomenon in sheep and Snyder (1937) has shown that carbon particles introduced into the amniotic sac of a rabbit foetus were immediately distributed through the lungs but if the foetus were made apnoeic *in utero* by an injection of pentothal sodium the lungs were free of carbon particles. Other conclusive evidence of the presence of intra-uterine respiration has been shown by the work of Davis and Potter (1946).

Intranatal respiration therefore explains the mechanism of the development of pneumonia in the stillborn infant in cases where the membranes have been ruptured some time and the labour is prolonged. The rupture of the membranes and the introduction of bacteria into the liquor is a *sine qua non* of its development. Obviously if bacterial growth can be inhibited in the liquor the development of intranatal pneumonia and pneumonia in the newborn resulting from intra-uterine pulmonary infection will be prevented.

Despite the improvement in the stillbirth and neonatal death rates (foetal) deaths from intra-uterine infection still occur.

F. J. Browne in 1922 in reviewing 153 cases of neonatal death found at autopsy that pneumonia was the cause in 31 per cent. He also drew attention to the fact that 5 cases of stillborn babies had evidence of intra-uterine pneumonia.

Douglas and Stander (1934) took blood cultures from the heart of stillborn infant immediately following delivery and found that the great majority of blood cultures were positive in infants born following prolonged labour where there was definite evidence of intra-partum infection. They defined prolonged labour as a labour of 30 hours or more. In many instances premature rupture of the membranes was present before labour was established and in due course evidence of infection in the vaginal discharges was noted. In over half such cases histological examination of the placenta revealed an acute and active infection.

Stander also noted that operative delivery, puerperal infection, maternal morbidity and foetal mortality were greatly increased if the labour lasted 60 hours or more. The organism most commonly isolated in these cases was the anaerobic streptococcus.

Labate (1947) in 637 autopsies upon viable foetuses and neonatal infants observed pneumonia in 8 per cent, massive aspiration of amniotic fluid in 18 per cent and hyaline membrane in less than 1 per cent.

Siddall (1950) stated that in cases of prolonged labour evidence of leucocyte inflammatory infiltration of the placental amnion, chorion and umbilical cord could be illustrated and these cases showed an increased incidence of post-partum infection in the mother.

Corner *et al.* (1951) reviewed the foetal mortality in cases of prolonged labour at the Boston Lying-In Hospital and found that 6·6 per cent of foetal deaths were due to infection from one of the following organisms: *Staphylococcus pyogenes*, *Bacterium coli*, Pneumococcus or anaerobic streptococcus.

From the above observations it is obvious than an antibiotic which will reach the infant via the maternal blood stream promptly and in high therapeutic concentration will improve not only

the foetal salvage rate but also safeguard the mother against puerperal pelvic infections.

Varying opinions regarding the diffusibility of drugs as well as antibiotics across the placenta to the foetus have been expressed from time to time. Siddall (1950) and Eastman (1952, 1953) express doubt that penicillin for example is effective against intra-uterine infection of the foetus. On account of these and other conjectural opinions regarding the transference of antibiotics to the foetus controlled clinical trials were carried out in the Obstetric Unit of Hammersmith Hospital.

Methods of Investigation

A. All cases in which for obstetrical reasons, artificial rupture of the membranes was performed

The antibiotic chosen was administered between 2 and 6 hours before the surgical induction of labour was performed. At the time of the surgical induction samples of liquor amnii and maternal blood were collected. At the time of delivery samples of maternal blood, cord blood and mucus from the baby's throat were collected.

B. Cases of elective Caesarean section

At a known time before operation the antibiotic under trial was administered to the mother and at operation samples of liquor amnii, cord blood and maternal blood were collected.

C. Cases of "prolonged labour"

In all cases of "trial labour" or incoordinate uterine action after the membranes had been ruptured for some hours a vaginal swab was cultured and an antibiotic administered to the mother. At delivery the following specimens were collected: (1) mucus from the baby's throat; (2) maternal blood; (3) cord blood.

The specimens of blood obtained in all the above procedures were allowed to clot and the serum then separated by centrifuging. The antibiotic under surveyance was then assayed by a microbiological method using a standard organism. All assays were performed by making serial dilutions of the serum or amniotic fluid in nutrient broth, using 1·0 ml. volumes, and then adding one drop (1/1000 dilution) of a suitable suspension of a sensitive organism. The results were read after overnight incubation at 37° by turbidity, the highest dilution of test fluid showing no turbidity being recorded as the inhibitory dilution.

The results in some cases were controlled by a similar series of tubes containing known concentrations of the antibiotic under trial, in order to assess the absolute amount of antibiotic present in the undiluted serum or amniotic fluid.

The "Oxford" strain of *Staph. pyogenes* was used as the test organism for the assay of Penicillin concentration. For assay of all the other antibiotics, a mutant of *Bact. coli* strain K12 which requires threonine, leucine, and thiamine (mutant W677) was employed.

In the case of Penicillin and Aureomycin a glucose broth was used, as the inhibitory dilution of these antibiotics is best defined in an acid medium (Aureomycin pH 6·6).

The dosages of the antibiotics used were:

Penicillin 1,000,000 units.
Streptomycin 1·0 g.
Chloramphenicol 500 mg.
Aureomycin 500 mg.
Terramycin 500 mg.

After the initial dose was administered no further therapy was given except in cases of prolonged labour. Five groups of 10 patients were each given different antibiotics.

Results

(a) *Penicillin.* The liquor amnii recovered from artificial rupture of the membranes in all cases showed a high concentration of Penicillin and it was queried whether a bacteriolysin was not present in the liquor to account for these findings. It was difficult to put up a further control using penicillinase which would nullify the effect of penicillin if present in the liquor amnii.

The tubes set up were as follows:

Tube 1: Nutrient broth, liquor, broth culture of Oxford *Staphylococcus pyogenes.*

Tube 2: Nutrient broth, liquor, broth culture of Oxford *Staphylococcus pyogenes* and Penicillinase.

It was found that turbidity occurred in all dilutions of Tube 2 and it was concluded that the

staphylococcus was inhibited by penicillin and not by a bacteriolysin or any other component of the liquor amnii.

At the time of delivery samples of cord blood and maternal blood were collected in all cases and the serum assayed for Penicillin. The results in all 10 cases were consistent and are tabulated in Tables I and II.

TABLE I

Case	Injection–Induction Interval	Liquor Amnii	Maternal Blood	Ratio
A	3 hours 20 minutes	1/64	1/32	2:1
B	3 hours 45 minutes	1/64	1/64	1:1
C	4 hours 5 minutes	1/64	1/8	8:1
D	4 hours 30 minutes	1/64	1/16	4:1
E	5 hours 25 minutes	1/64	1/8	8:1
F	6 hours 50 minutes	1/64	1/8	8:1
G	8 hours 10 minutes	1/64	1/4	16:1
H	9 hours 40 minutes	1/64	1/2	32:1
I	11 hours 20 minutes	1/64	1/2	32:1
J	12 hours 20 minutes	1/16	0–½	16:1

These results are illustrated in Figure 1.

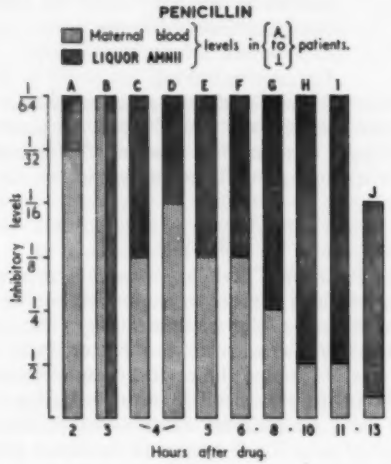

FIG. 1

The presence of a high level of penicillin in the liquor amnii was further evaluated by giving one patient 1,000,000 units of Penicillin by intramuscular injection and withdrawing liquor amnii at intervals by abdominal paracentesis and at the same time taking samples of maternal blood. The results so obtained are recorded in Fig. 3 and Table III.

TABLE II

Case	Injection–Delivery Interval	Maternal Blood	Cord Blood
A	3 hours 45 minutes	1/32	1/8
B	6 hours 27 minutes	1/16	1/8
C	8 hours 10 minutes	1/8	1/4
D	8 hours 45 minutes	1/8	1/4
E	9 hours 45 minutes	1/8	1/4
F	10 hours 15 minutes	½–1	½
G	10 hours 30 minutes	0–½	0–½
H	11 hours 5 minutes	0	0
I	11 hours 20 minutes	0	0
J	12 hours 40 minutes	0	0

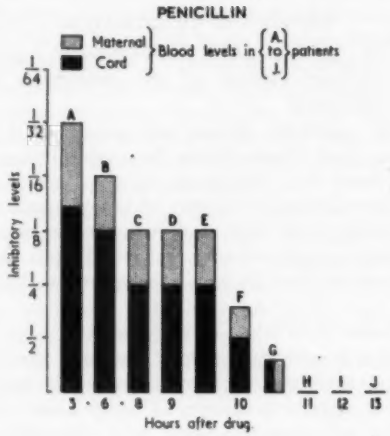

FIG. 2

TABLE III

Time Interval since Injection	Maternal Blood Level	Liquor Amnii Level
2 hours 15 minutes	1/128	1/128
2 hours 50 minutes	1/128	1/128
3 hours 50 minutes	1/64	1/128
4 hours 20 minutes	1/64	1/128
6 hours	1/16	1/128
7 hours 30 minutes	1/4	1/128

A further case illustrates the use of Penicillin to combat intranatal infection. This patient was admitted on 22nd November, 1952 in labour.

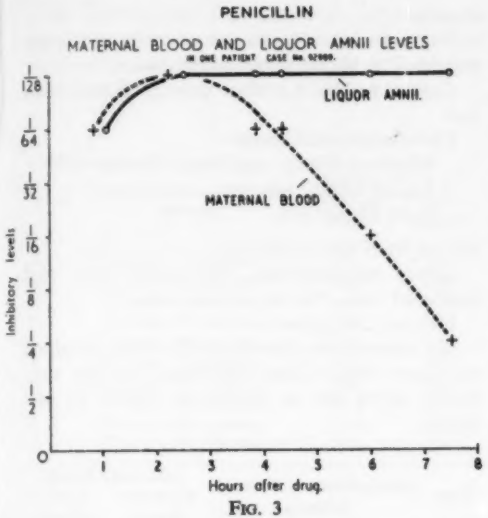

FIG. 3

She had been in labour since 2 a.m. and despite good uterine contractions little progress was noted and at 10 p.m. the membranes ruptured spontaneously. The foetus presented as a vertex in the right occipito-posterior position (on 23rd November, 1952 at 9.30 p.m. the maternal temperature was 99·8; pulse 110 and respirations 22). The foetal heart sounds were audible and regular at 140 beats per minute. The patient was placed on Penicillin 500,000 units 6-hourly and a vaginal swab was plated. The culture obtained was a profuse growth of *Staphylococcus pyogenes* and a scanty growth of *Bacterium coli*.

The patient's condition remained good and labour was allowed to progress. On 24th November at 7.30 p.m. a Caesarean section was performed on account of maternal distress and no progress in labour. At the time of the Caesarean section liquor amnii, cord blood and maternal blood were obtained and assayed for Penicillin levels. The last injection of Penicillin was given at 3.30 p.m. (4 hours before delivery).

Further mucus from the baby's pharynx was examined and direct microscopy revealed "scanty pus cells and epithelial cells but no organisms". No growth was obtained on culture.

Results	Liquor Amnii	Cord Blood	Maternal Blood
Inhibitory levels ..	1/32	1/4	1/8

In the case described the total duration of labour was 65 hours 30 minutes and the membranes had been ruptured 45 hours 30 minutes.

The puerperium was uneventful and afebrile and the baby did well.

(b) *Streptomycin.* Table IV and Fig. 4 give the results obtained in a further 10 patients using Streptomycin as the antibiotic under surveyance.

The amount of Streptomycin in the liquor amnii was almost non-existent in all cases.

(c) *Chloramphenicol.* Table V and Fig. 5 represent the inhibitory levels obtained in the

TABLE IV

Case	Injection–Delivery Interval	Inhibitory Levels Maternal Blood	Cord Blood
A	1 hour 45 minutes	1/32	1/16
B	3 hours	1/32	1/16
C	3 hours 15 minutes	1/64	1/16
D	4 hours 50 minutes	1/32	1/16
E	8 hours 10 minutes	1/64	1/16
F	12 hours 15 minutes	1/64	1/32
G	12 hours 20 minutes	1/64	1/32
H	13 hours 10 minutes	1/64	1/32
I	18 hours 10 minutes	1/32	1/32
J	20 hours	1/8	1/4

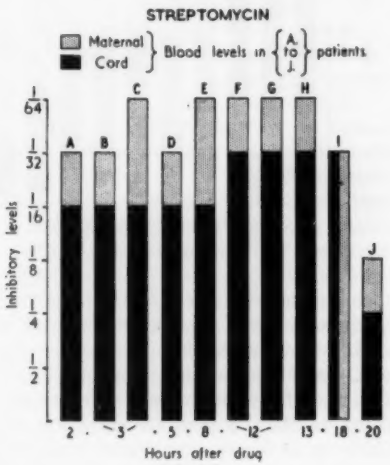

FIG. 4

maternal blood and cord blood at delivery after the patient had received an initial dose of 500 mg. of Chloramphenicol by mouth. In the majority of cases there was no evidence of Chloramphenicol in the liquor amnii and when present it was a negligible amount.

TABLE V

Case	Administration–Delivery Interval	Inhibitory Levels Maternal Blood	Cord Blood
A	2 hours 15 minutes	1/64	1/16
B	4 hours 10 minutes	1/64	1/16
C	5 hours 10 minutes	1/64	1/16
D	6 hours 45 minutes	1/32	1/8
E	9 hours 10 minutes	1/32	1/8
F	10 hours 10 minutes	1/32	1/8
G	11 hours 30 minutes	1/32	1/8
H	14 hours 10 minutes	1/32	1/8
I	18 hours	1/16	1/4
J	20 hours 20 minutes	1/8	1/2

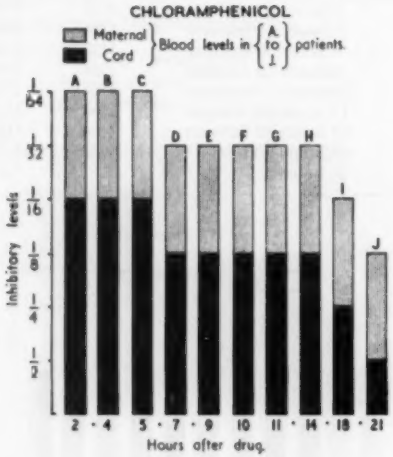
CHLORAMPHENICOL
Maternal
Cord
Blood levels in A. to J. patients.
A B C D E F G H I J
1/64 1/32 1/16 1/8 1/4 1/2
Inhibitory levels
2 · 4 5 · 7 · 9 10 11 · 14 · 18 · 21
Hours after drug.

FIG. 5

One patient who had a fulminating toxaemia of pregnancy had a surgical induction of labour on 25th November, 1952 but labour did not ensue. Forty hours later a vaginal swab was taken and the patient given Chloramphenicol 500 mg. orally at 2 p.m. The dose was reduced to 250 mg. at 8 p.m. and the baby delivered at midnight by lower segment Caesarean section.

Results

Vaginal swab: Numerous pus cells and gram negative bacilli on direct examination.

Culture yielded a profuse growth of *Bacterium coli.*

Chloramphenicol assay:

Maternal blood: inhibitory dilution 1/32

Liquor amnii: nil

Cord blood: 1/8.

Mucus from baby's pharynx

Direct examination: Numerous pus and epithelial cells. No organisms seen.

Culture: No growth.

(d) *Aureomycin.* Similar results were obtained to those when Chloramphenicol was the antibiotic under test as shown by Table VI and Fig. 6.

TABLE VI

Case	Administration–Delivery Interval	Inhibitory Levels Maternal Blood	Cord Blood
A	2 hours 15 minutes	1/16	1/8
B	4 hours	1/64	1/32
C	4 hours 15 minutes	1/32	1/16
D	6 hours 5 minutes	1/64	1/32
E	7 hours 10 minutes	1/64	1/32
F	10 hours 5 minutes	1/32	1/16
G	12 hours	1/32	1/16
H	15 hours 15 minutes	1/32	1/16
I	17 hours	1/32	1/16
J	17 hours 55 minutes	1/16	1/4

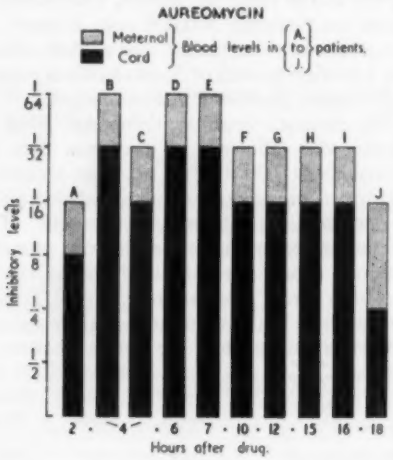
AUREOMYCIN
Maternal
Cord
Blood levels in A. to J. patients.
A B C D E F G H I J
1/64 1/32 1/16 1/8 1/4 1/2
Inhibitory levels
2 · 4 · 6 7 · 10 · 12 · 15 16 · 18
Hours after drug.

FIG. 6

(e) *Terramycin.* This antibiotic behaved in a similar manner to the other orally administered antibiotics and the results are given in Table VII and Fig. 7.

TABLE VII

Case	Administration–Delivery Interval	Inhibitory Levels Maternal Blood	Inhibitory Levels Cord Blood
A	2 hours 15 minutes	1/16	1/8
B	3 hours 30 minutes	1/64	1/32
C	3 hours 45 minutes	1/32	1/16
D	3 hours 50 minutes	1/64	1/16
E	7 hours 40 minutes	1/32	1/16
F	9 hours 15 minutes	1/32	1/16
G	10 hours 15 minutes	1/32	1/16
H	17 hours 10 minutes	1/16	1/8
I	18 hours 20 minutes	1/16	1/8
J	19 hours 20 minutes	1/8	1/4

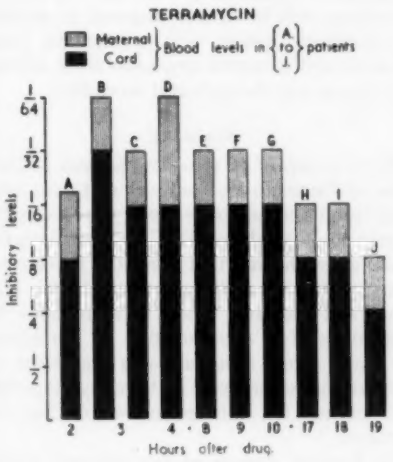

FIG. 7

DISCUSSION

The placental transmission of antibiotics is allied to the behaviour of these drugs in the body and it is well to consider this fact. It is known that Streptomycin, Aureomycin and Terramycin are rapidly distributed in the extracellular fluid space and Penicillin and Chloramphenicol appear to be distributed throughout a large space as they are found in low concentration in certain cells and thereafter penetration occurs into various organs. The concentrations obtained differ not only with the various organs but also with each antibiotic.

Information regarding the distribution throughout the body is incomplete except in the case of the cerebrospinal fluid and liver. Penicillin hardly penetrates the blood-brain barrier even when the meninges are inflamed except when frequent large doses are given. Terramycin behaves in a similar manner in that almost none can be found in the cerebrospinal fluid. Streptomycin gives concentrations varying between $\frac{1}{8}$ and $\frac{1}{10}$ those obtained in the plasma in a few hours, Aureomycin $\frac{1}{2}$ to $\frac{1}{8}$ after a period of several days and Chloramphenicol gives concentrations about $\frac{1}{8}$ to $\frac{1}{4}$ in a short space of time.

All five substances are excreted by the kidney. Penicillin and Terramycin are recovered in high proportion from the urine (about 75 per cent) while only about 50 per cent of Streptomycin can be recovered in this way. Chloramphenicol behaves in a different way in that only about 10 per cent is recoverable as Chloramphenicol although about a further 80 per cent is excreted in the form of inactive breakdown products. Aureomycin is only recoverable to about 15 per cent of the original dose. Penicillin is eliminated both by glomerular filtration and tubular excretion. Tubular blocking agents, therefore, may be used to prolong the blood levels by preventing excretion. The other antibiotics are excreted by glomerular filtration and the rate of elimination is independent of urinary output and dependent only on blood concentration.

It is also worth mentioning that the molecular weights of these agents are in the neighbourhood of 440 and being small molecules should pass the placental barrier. However, there has been a great deal of controversy regarding placental transference of antibiotics and early experiments on animals failed to show that Penicillin permeated from the maternal circulation to the foetus. In 1944 Green and Hobby gave 100,000 units of Penicillin to patients in active labour about 2 hours before delivery and found that the cord blood level was approximately $\frac{1}{4}$ that of the maternal blood level but they found no evidence of Penicillin in the liquor amnii. Similar results were obtained by Herrell *et al.* (1944) and

Hutter and Parks (1945). The first evidence that a significant amount of Penicillin was present in the liquor amnii after giving systemic Penicillin to the mother was the work of Woltz and Zintel (1945) although they made no attempt to correlate the liquor and maternal blood concentrations. In all investigations so far performed there is a marked individual variation from case to case as regards the maternal and foetal blood concentrations but no evidence that the liquor amnii concentration remains at a high level for a considerable period of time despite a drop in the maternal blood level. Braitenberg (1952) believes that the concentration of Penicillin in the foetal circulation varies with the maternal temperature and weight. In the present series larger doses of Penicillin were used and this may account for the consistent results and further the liquor amnii was collected using full aseptic precautions and thus facilitating a true estimation of the liquor concentration.

The high titre of Penicillin in the liquor can be explained by the rapid renal excretion of Penicillin by the foetus thus also lowering the serum level. Alternatively Penicillin is absorbed by lipid substances and thus may be absorbed by the amnion which then liberates it into the liquor. The fact that Penicillin is excreted in high concentration by the foetal kidney is the most likely answer as 75 per cent of systemic Penicillin is excreted unaltered by the kidney. However although this theory will account for the absence of Chloramphenicol and Aureomycin in the liquor amnii it does not account for the absence of Terramycin and Streptomycin; in fact one has to assume that the behaviour of Penicillin in this respect is one of selective absorption by the amnion or another variable property of the antibiotic.

This property of Penicillin can also aid in the investigation of the origin of the liquor amnii and will be discussed at length in a later communication.

The results obtained with the antibiotics are consistent with the works of other investigators and there can be no doubt that the placental transmission of antibiotics will lower the perinatal mortality if intra-partum infection is present.

In cases of intra-uterine infection during labour and intra-uterine foetal pneumonia the clinician may only infer which may be the aetiological organism from among the many species usually present. Bowie (1954) investigated 400 cases of puerperal pyrexia where high vaginal swabs were performed and found the organism in question was *Bact. coli* in 43 per cent of cases, enterococcus in 27 per cent of cases and staphylococcus in 11 per cent of cases. He stated that during the past 6 years the staphylococcus had become more important than any other potential pathogen commonly present in high vaginal swabs and states the "staphylococcus had inherited the ability to resist any antibiotic in clinical use". It is thus of great importance if the patient and her foetus are to benefit from antibiotic therapy in cases of prolonged labour with ruptured membranes that high vaginal swabs should be plated within 24 hours of rupture of the membranes and thus the means will be at our disposal to prescribe the antibiotic which will protect the foetus, placenta and maternal organism from infection and thus lower the perinatal mortality.

Summary

(1) A group of 10 patients received 1,000,000 units of Penicillin and samples of liquor amnii, cord blood and maternal blood were assayed by a microbiological method for the antibiotic. These cases showed that Penicillin traverses the placental barrier and was present in the liquor amnii and the cord blood in therapeutic concentrations. The concentration of Penicillin in the liquor amnii remained at a high level after the maternal serum level had greatly diminished. The reason for this phenomenon has been discussed.

(2) Further groups of ten patients received Streptomycin, Chloramphenicol, Aureomycin and Terramycin. All these antibiotics are transferred from the maternal to the foetal organism and in therapeutic concentrations. The liquor amnii contained negligible amounts of these substances and it is concluded that the amniotic membrane has some selective absorptive capacity for Penicillin.

(3) To obtain the optimum effect of antibiotic therapy in cases of prolonged labour with ruptured membranes it is essential that all cases

where the membranes have been ruptured 24 hours high vaginal swabs should be plated.

The author is greatly indebted to Dr. W. Hayes, Reader in Bacteriology, who carried out the microbiological assays of the antibiotics. I wish to express my thanks to Professor J. C. McClure Browne under whose guidance this investigation was carried out, also to Mr. Ian Donald and Mr. J. Duncan Murdoch in allowing me access to their patients. Finally I should like to thank the nursing staff of Hammersmith Hospital for their help.

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HISTOCHEMICAL CHARACTERIZATION OF THE SPECIFIC CELLS IN PAGET'S DISEASE OF THE VULVA

BY

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THOUGH the occurrence at other sites of a skin lesion similar to Paget's disease of the nipple was noted by Paget himself in his original paper (1874), it remained a somewhat nebulous entity till reviewed by Weiner in 1937. This author showed that the lesion had a specific histology and was confined to the apocrine areas, and he supported the view that it was related to an underlying carcinoma of the apocrine sweat glands in much the same way that Paget's disease of the nipple is related to an underlying intra-duct carcinoma. Though 7 of the 16 cases accepted by Weiner were non-vulval, all but one of the cases we have found recorded since that date occurred in the vulva or in the perineal region of women: these are the cases of Miduno (1940), Traub (1943), Jeffcoate, Davie and Harrison (1944, Case II), Lübschitz (1944), Casper (1948), Foraker and Miller (1949), Di Prisco and Convit (1948), Ahumada (1950, quoted Huber *et al.*), Huber, Gardiner and Michel (1951, 3 cases), Sonck (1951), Vermenouze (1951), and Paget, Rowley and Woodcock (1954). Casper's main case is a later report on Traub's, but he adds a brief account of a second case, on which a promised report by Wager has not appeared. Though we have been unable to read Komori's (1938) text, we find his photomicrographs unconvincing. Parsons and Lohlein (1943) record one case on the scrotum. A total of 15 cases has thus been added to Weiner's 16. The majority of these authors have favoured Weiner's views, but Jeffcoate *et al.*, like Willis (1953), deny the specificity of the lesion.

Our object in reporting one additional case is to draw attention to the finding of mucin in the characteristic cells of these lesions. While this paper was under preparation the appearance of Paget *et al.*'s paper, which mentions this finding for the first time (the material recorded by Eversole (1952) in his case (*v.inf.*) must surely have been glycogen) removed any claim we might have had to originality. Nevertheless, we believe that the evidence we can present for the constancy of the phenomenon, which may well give it diagnostic value, and the significance given to it by its relation to our earlier work on mucin in sweat gland tumours justifies our persevering in this report.

CASE HISTORY

Clinical history. A woman of 68 presented herself for the first time to Professor J. C. McClure Browne at this hospital in January, 1953 with a complaint of severe vulval and peri-anal irritation, of 13 years duration in all. She was seen by a gynaecologist at another hospital in 1944, and a diagnosis of leukoplakia was made. Treatment by palliative measures, including X-rays, was ineffective, and in 1948 a partial vulvectomy was performed. Complete relief was experienced for 2 years, but symptoms returned in 1950 and became steadily more severe.

General examination on her first appearance here showed an obese, well-preserved elderly woman with mild hypertension but no other disease apart from the local condition. The skin of the whole vulva area, extending backwards to the peri-anal region, was thickened, indurated and whitish (Fig. 1). There were scratch marks but no deep cracks or fissures. The margin of the lesion was fairly well defined in most areas but was not especially prominent. The original vulvectomy appeared to have been limited to the anterior part of the right labia, and the disease was now most marked

on the other side. A diagnosis of leukoplakia vulvae was made.

Professor Browne performed a simple vulvectomy on 9th January, 1953, excising all the affected area and suturing vaginal mucosa to healthy skin. The immediate result was very satisfactory but at present (March, 1954) there is some suspicion of marginal recurrence.

Pathology. Part of the records of the patient's first hospital admission elsewhere in 1948 have been lost, and the gynaecologist concerned has since died. We have been unable to obtain any description of the tissue removed at that time.

The specimen received in 1953 measured 95×70×20 mm. and consisted of the whole vulva. Naked eye examination added nothing to the clinical description: careful search failed to show any deep involvement.

Microscopically (Figs. 2 and 3) the picture of the lesion is uniform throughout. The epidermis in general is thickened, with hyperkeratosis, acanthosis, and large crowded rete pegs which are both thickened, lengthened and irregular. There is marked subepidermal cellular infiltration. The pattern of the whole is so much like that of a severe leukoplakia that the clinical diagnosis of that condition seems most natural.

Within this abnormal epidermis there are many Paget cells. The characteristics of these cells have been many times described and need not be laboured here. They lie chiefly in the juxta-basal layer of the epidermis, but are occasionally found more superficially. They are found frequently in the outer sheaths of hair follicles, and once only in the superficial part of a sweat gland duct (the rest of the gland being unaffected). Towards the periphery of the lesion they decrease in number, and the leukoplakia-like thickening of the epidermis decreases in step. Most of the specimen was cut up into serial blocks at approximately 3 mm. intervals, but no evidence of any deeper invasion was found. It was shown in this manner however that Paget cells could be identified in skin that had been regarded clinically as normal near the margin of the lesion, and that at several points the margin of excision was dangerously narrow.

Histochemistry. The details and significance of the individual histochemical reactions employed are discussed elsewhere (Lennox, Pearse and Richards, 1952; Pearse, 1953). The cytoplasm of the specific cells stains a deep red (less however than the maximum attainable) with the periodic-acid Schiff reaction (Fig. 4). This reaction is not abolished by treatment with diastase. The material is not metachromatic to aqueous toluidine blue. It stains well with Alcian blue, and is weakly Gram-positive. It binds methylene blue at pH 3·6 and above. It contains no sudanophile material. It stains incidentally fairly well with Southgate's mucicarmine.

These findings bring the material present into the group of "epithelial" mucins of Table II of Lennox, Pearse and Richards, though it is rather more acidic than any of those included there.

Discussion

In Paget *et al.*'s case (1954) (the only previous example in which it seems to have been looked for), PAS-positive material was demonstrated in the Paget cells. It was found in the present case: we can add 2 other cases of typical Paget's disease of the vulva in which we have been able to examine slides, but which, owing to insufficient data, we have not thought proper to report in detail here. It seems probable therefore that most, if not all, cases of extra-mammary Paget's disease will be found to show this (under the circumstances) highly specific reaction.

A considerable experience in the study of skin tumours using this and other reactions for mucins (Lennox, Pearse and Richards, 1952; Lennox, Pearse and Symmers, 1952; Lennox, 1954a) has shown that mucin in any quantity in a skin tumour is an almost invariable sign of sweat gland origin. Metastatic adenocarcinoma, and a few tumours of the rodent group (which latter show only slight amounts at most) form the only exceptions. Under no circumstances does the epidermis, or any of the tumours derived directly from the epidermis, produce mucin. Hence we may conclude that the Paget cells are not of epidermal origin, and that they are almost certainly of sweat gland origin.

In our own case we assume that a small hidradenocarcinoma was present in the part of the vulva removed in 1948. In other cases (such as Weiner's) a frank invasive carcinoma with metastases was present. In others (such as Sonck's, and Parson and Lohlein's) a multi-

centric intraduct tumour of numerous sweat glands was present. In yet others none has been found. But when we recollect that in Paget's disease of the nipple the frequency of discovery of intraduct carcinomata of the breast has depended largely on the care with which the specimens are examined (Muir, 1927, 1939), and when we add to this the fact that in theory at least an intraduct carcinoma of a single sweat gland might give rise to the most extensive epidermal involvement, we must conclude that a rigorous demonstration of the absence of sweat gland lesions in a case of extra-mammary Paget's disease will involve complete serial sectioning of the whole affected area. This might be possible in an early case, but has not yet been attempted to our knowledge.

This observation should remove the last excuse for those who continue to confuse Bowen's disease and Paget's disease. It has always seemed obvious to us that the first is a disorder of the epidermis as a whole, a squamous "carcinoma *in situ*", and the second a reaction of the epidermis to exogenous cells of a manifestly different race: the presence of mucin in these exogenous cells only emphasizes their foreignness.

To enter into any detailed discussion of the mechanism of invasion by these foreign cells is no part of our purpose: much of what has been written of the nipple lesion (Inglis, 1946, and Willis, 1953, present opposed views of this) applies here. We believe that our findings support what one may call the Muir view of the matter (Muir, 1927). The crux of the matter lies here: that such invasion only occurs when tumour reaches the epidermis via an epithelium with which it is in direct continuity, but which is sufficiently distinct to produce tumours of a readily distinguishable cytological type. Such sites are rare: at all the ordinary muco-cutaneous junctions epidermis joins squamous or transitional epithelium. Direct contiguity of epidermis and columnar epithelium occurs only round the nipple ducts and the sweat gland orifices: Paget's disease can hence arise only at these sites. That extra-mammary Paget's disease should be so pre-eminently vulval in distribution is a fact not easy to account for on these grounds: but one may equate it with the observation (Lennox, 1954b) that of all superficial hidradenomata (i.e., those involving the sweat gland ducts) nearly half are vulval.

The rule suggested above has few exceptions. Two cases of rectal carcinoma invading the perineal skin (Dunn, 1930; Pinkus and Gould, 1939) may represent a disregard by the adenocarcinoma of the narrow barrier of anal squamous mucosa between it and the epidermis. Eversole's case (1952) of invasion of the suprapubic epidermis by a bladder carcinoma is the only complete exception known to us. Imitation of Paget's disease by melanoma (Stout, 1938), in any case not a very close imitation, serves to prove the rule: for here we have a tumour of a foreign cell arising actually within the epidermis.

The constancy (4 out of 4 cases known to us) of appearance of mucin in vulval cases is a little unexpected. The frequency of mucin in ordinary hidradenocarcinomata (Stout and Cooley, 1951; Lennox, Pearse and Symmers, 1952; additional unreported cases of our own) is probably of the order of 50 per cent. We would not be surprised to find some cases of extra-mammary Paget's disease in which mucin was absent. In ordinary Paget's disease of the nipple, we have examined 7 cases without finding a single example in which the specific cells contain mucin. But, despite the homologies between breast and sweat gland, mucin is much rarer in tumours of the former than the latter (Geschickter, 1943, gives a figure of 3 per cent for mucin secretion in breast carcinomata): so this difference between the two closely similar lesions is readily understood.

It seems to us in reading clinical accounts of the condition that its seriousness as a disease has been somewhat undervalued in comparison with its interest as a pathological curiosity. A very high proportion of reported cases in which adequate time has elapsed are known to have recurred, and though several have survived long enough to die of intercurrent disease a number (e.g., Weiner's) died of metastasizing carcinoma. This may serve to emphasize the need for prompt and wide excision, and since (as our case exemplifies) it cannot be diagnosed clinically in the majority of cases, it adds yet another argument to the case for biopsy in every case of resistant vulval "leukoplakia".

FIG. 1
The vulval lesion in January, 1953.

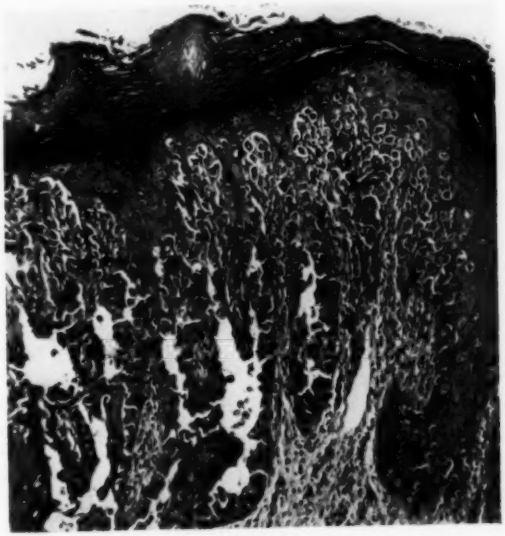

FIG. 2
The epidermal lesion. On the right Paget cells are scattered sparsely in a leukoplakia-like epidermis: on the left they are numerous enough to have almost broken it up. H. & E. ×120.

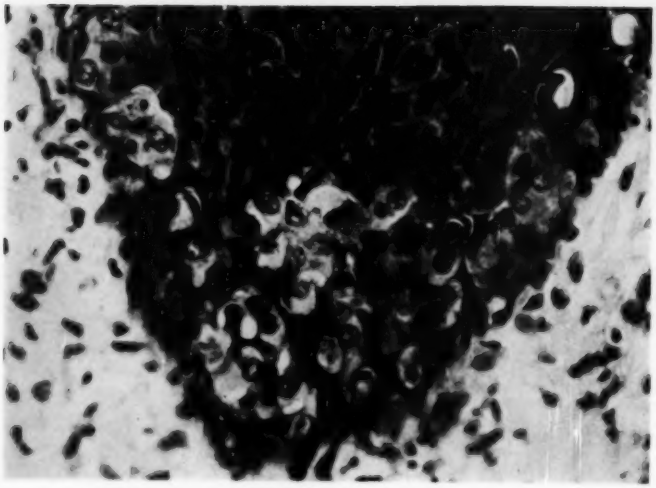

FIG. 3

Parabasal distribution of Paget cells deep in a hyperplastic hair follicle. H. & E. ×580.

FIG. 4

Mucin in Paget cells, every one of which is deeply stained. Periodic-acid Schiff. ×300.

B.L., A.G.E.P.

Summary

The occurrence of mucin in the specific cells of a case of Paget's disease of the skin of the vulva is described.

It is believed that this adds additional evidence for the sweat gland origin of the lesion and (since it is probably constantly present or at least very frequent in these cases) it may be of considerable value in histological diagnosis of the condition.

Addendum. Two further cases of extra-mammary Paget's disease have been published by Whimster, I. W. (*Hautarzt*, Berlin; **4**, 40, 1953: cases II and III), both perianal and one in a man. Mucin was demonstrated in the specific cells in both cases.

Acknowledgments

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DEFERRED NIDATION OF THE BLASTOCYST, WITH REFERENCE TO THE LENGTH OF GESTATION

BY

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THE knowledge that blastocysts do not need an immediate attachment to the uterus for their survival is not new; and the purpose of this note is to consider on a foundation of general biology in what way a delayed nidation might perhaps account for prolonged pregnancy in women.

In five different rodents Lataste (1891) noticed that gestation was prolonged if conception had occurred during lactation; and yet the newborn were of normal weights. He concluded that gestation had been retarded at its commencement. He also found that gestation might be extended for several days if a mouse had been injured soon after coitus. Daniel (1910), besides agreeing with Lataste's statements, discovered that the precise length of gestation in mice which had conceived during lactation depended on the number of young which were being nursed at the time of conception: if more than 3 were being suckled, gestation was prolonged approximately by one day for each additional nursling.

The ova of mice fertilized in these circumstances develop normally to the blastula stage on the 6th day, after which nidation is postponed without destruction of their viability (Kirkham, 1916). These various observations have been confirmed (King, 1913; Enzmann, Saphir and Pincus, 1932; Enzmann, 1935) and it has been noted incidentally that until nidation has taken place, though not afterwards, the ova are readily killed by oestrogen (Burdick and Pincus, 1935; Pincus, 1936).

In many species a greatly delayed nidation of the blastocyst is a regular, healthy occurrence. Hamlett (1935) says that in the armadillo (*Dasypus novemcinctus*) ovulation follows mating in the middle of July, and a blastocyst which has formed a few days later lies dormant until November when it becomes attached to the uterus and development of the embryo is resumed. A similar normal postponement of nidation, lasting it may be for several months, has been observed as the usual occurrence in the marten, bear, weasel, shrew, roedeer, badger, and several kinds of seal.

According to Fischer (1931) and Neal (1948) the badger mates in July or August, and nidation of the ova does not take place until January; and in a note on the Grey Seal (*Halichoerus grypus*) of these islands, Backhouse (1954) says that the female is impregnated some 3 weeks after parturition, so that her gestation period is nearly a year. Referring to deer, Bayon (1951) made the interesting suggestion that delayed nidation of the blastocele may perhaps explain William Harvey's mistake in supposing that among the deer of Windsor forest fertilization might happen without contact between hart and hind.

My own interest in the subject arose from the fact that mice and rats in our animal rooms at the Chester Beatty Research Institute occasionally bore two successive normal litters after a single mating (Burrows, 1941). Among 473 consecutive pregnancies in our Wistar rats the phenomenon was recorded in 10. The same event occurred now and then in mice but a numerical account was not kept. Scientists to whom the happening was described regarded it as incredible. However the observations were correct, having been confirmed in other institutions, and in fact the phenomenon had already been recorded by animal breeders (Pickard, 1928; du Boisson, 1939).

At first I thought that perhaps spermatozoa had survived in one of the oviducts of a bicornuate uterus throughout pregnancy and had

fertilized ova of the post-parturitional oestrus; for it had been shown that spermatozoa retained their potency in an isolated rabbit's epididymis for as long as 38 days (Hammond and Asdell, 1926). Nevertheless this hypothesis was incorrect and the true explanation was shown by Bloch (1952) to be the retention of some of the blastocysts in the oviducts and their survival in a dormant state throughout pregnancy after which they might enter the uterus and develop as a second litter. Her article is accompanied by excellent photomicrographs.

The co-existence of healthy unattached blastocysts with growing embryos may account for such examples of superfoetation as the following: a sow gave birth to 10 piglets on 5th November and 26 days later she produced a second litter of 10 (Buie, 1953). In another instance a sow had one piglet at term and 21 days later gave birth to a litter of 8 (Smythe, 1953). In each case there had been only one mating.

From the facts quoted above it seems reasonable to suspect that a woman, too, may be subject occasionally to a delayed nidation of the blastocyst; and the possibility, it seems, ought to be considered in connection with the duration of pregnancy. The medico-legal aspects of the affair will be fully appreciated, and in view of the facts few of us would be willing to declare on oath what, in a woman, are the limits of a healthy gestation.

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AN ANALYSIS OF THE MATERNAL AND FOETAL WEIGHT FACTORS IN NORMAL PREGNANCY

BY

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ALMOST a century has passed since Gassner (1862) focused his attention on maternal weight gain during pregnancy. Since that time a great deal has been written concerning the maternal and foetal weight factors in pregnancy, though much that has been written is of little statistical value due in part to an inadequacy of numbers and in part to generally faulty statistical technique.

The majority of workers suggest that toxaemic patients tend to gain more weight than normally pregnant women (Chesley and Chesley, 1943; Dawson and Borg, 1949; Evans, 1937; Hamlin, 1952; Harding and Van Wyck, 1934; McIlroy and Rodway, 1937; Stander and Pastore, 1940; Wodon, 1935; Zangemeister, 1916), and with this in mind all toxaemic patients have been excluded from the survey. It was felt that a statistically acceptable analysis of the maternal and foetal weight factors in normal pregnancy was desirable as a basis for much research that has yet to be done on pathological weight gain, water retention, adrenal control of water and nitrogen balance, etc.

MATERIAL

The material under consideration consists of 1,000 normal mothers who were delivered of 1,002 babies. It should be stated at the outset that all cases were booked and delivered in hospitals in Cardiff and Crickhowell, and for this reason they are not a true cross section of all the births in the country. They were, however, a random sample of hospital patients delivered since 1944.

The standards of normality were as follows:

(i) The mother's first antenatal visit was at or before 12 weeks' gestation. (This eliminated large numbers.)

(ii) There was no pre-existing disease in any major system in the mother. Patients with thyrotoxicosis, tuberculosis, chronic renal disease, diabetes mellitus, cardiac defects, essential hypertension, etc., were all excluded.

(iii) There was no toxaemia of pregnancy.

(iv) Delivery took place within 20 days of the expected date. (This may seem a rather liberal variation, though it does only represent 2 days for each lunar month of pregnancy, a very reasonable variation from the normal cycle of menstruation. If pregnancy is represented by 10 missed periods, up to 20 days' error might be expected on this basis.)

(v) The last antenatal visit took place within a maximum of 7 days of delivery.

(vi) A normal live baby (or babies) was produced.

Two Caesarean sections at term were included, as they were performed for simple disproportion due to contracted pelvis in otherwise normal women. Two sets of twins were included and in all calculations, except those relating to the weights of individual children, their weights were summated. Thus, in comparing weight gain in pregnancy, for example, with birth weight, the combined weight of both babies is regarded as the birth weight. In assessing the mean weight of boys and girls separately the weights are necessarily separated.

In estimating the weight gain during pregnancy from the twelfth week one makes use of the assumption of Kerr (1943) and other writers that the weight at this time is about equal to the pre-pregnant weight of the mother. The weight gain, therefore, from the twelfth week to term represents the total weight gain during pregnancy. A variety of different figures of gain and loss are given as the weight changes which occur in pregnant women between conception and 12 weeks. Chesley (1944) reviewing a series of

eight papers, gives the weight increase in the first trimester as 2·5 pounds in spite of the anorexia and vomiting which so frequently occur during this period. Cummings (1934), perhaps the most frequently quoted author on this matter, states that "43·5 per cent of the patients observed had gastric disturbances and lost 2-10 pounds, while 56·5 per cent were normal and showed slight gain in weight". He quotes 0·45 pound as being the approximate mean gain in the first trimester, and his assessment is based on the patient's statement of her normal weight before pregnancy.

For my purpose I have taken the weight at 12 weeks as being equal to the pre-pregnant weight for the following reasons:

(1) That a patient should know her pre-pregnant weight to within 0·45 pound, when the contents of the stomach, bowel and bladder make it so variable to within 2 pounds, seems unlikely.

(2) A number of authors report a small variable weight loss in the last days of pregnancy (Cummings, 1934; Dawson and Borg, 1949; Evans, 1937; Kemper, 1924b; Mahnert, 1924; McIlroy and Rodway, 1937; Momm, 1920; Siddall and Mack, 1933; Stander and Pastore, 1940).

It would seem pointless, in view of this, to add a small arbitrary weight at one end of pregnancy, and subtract a similar small arbitrary weight at the other, as the patients were not weighed immediately before delivery.

All ages quoted represent the age of the patient on the last birthday prior to her first antenatal visit.

The duration of labour was also recorded. The actual time of starting labour is notoriously difficult to assess as such a variety of symptoms and signs may herald its onset. In this series labour was deemed to have started at the time when the patient became aware of regular pains. The time was then measured to the birth of the baby.

In all cases the maternal weight gain was recorded in pounds and also as a percentage of the maternal weight at 12 weeks (or as a percentage of the pre-pregnant maternal weight, on the basis of the arguments already quoted). The weight of the baby was likewise recorded in pounds, and as a percentage of the maternal weight gain.

All cases, being delivered in the latter part of the war or early post-war years, were on a more or less fixed diet with regard to vitamin supplements and rationed foods, much more so than would have been possible in a similar survey in pre-war days when diet was less under the control of external circumstance. Gross variation in diet was therefore eliminated as far as possible, thus creating reasonable experimental conditions.

Maternal Weight Gain During Pregnancy

The mean weight gain during normal pregnancy is stated variously by different authors to be between 13 and 30 pounds. Stander and Pastore (1940), who give the highest figure, quote 13,96 Kg. (30·7 pounds) as being the average gain, but it should be noted that each of their patients received a quart of milk a day, which might account, at least in part, for the large weight increase. Hannah (1925), on the other hand, states that in a patient whose weight at the beginning of gestation is near standard, the gain should not be more than 14 pounds. He quotes 13 pounds 4 ounces as the mean normal gain. Bingham (1932) says that the average woman of medium size should not gain more than 15-20 pounds during her pregnancy, and Davis (1923) takes a similar view, but quotes 20 pounds as the high limit of desired weight gain (though his mean weight gain is 21 pounds and many normal women in his series must have gained more than 20 pounds). Kerr (1943) gives the mean gain as 22·9 pounds (in 500 primiparae), Evans (1937) quotes 16-18 pounds as normal gain, Slemons and Fagan (1927) give 16·5 pounds as the average maternal gain, Klein (1946) 21·05 pounds and Randall (1925) 22·5 pounds.

Table I shows briefly the gains recorded trimester by trimester.

The results for the present series are shown in Table II.

It will be seen that the figures for the present series bear a fairly close relationship to the mean of cases reviewed by Chesley (1944) covering 38 papers.

TABLE I

Author	Mean weight gain (pounds)				Mean gain in last trimester (pounds/week)
	1st Trimester	2nd Trimester	3rd Trimester	Total Gain	
Beardsley (1941)	0·8	12·4	11·6	24·8	0·87
Bingham (1932)	2·9	10·0	7·0	19·9	0·53
Cummings (1934) ..	0·45	13·13	10·5	24·08	0·79
Dawson and Borg (1949)	0·45 (assumed)	10·4	14·0	24·85	1·05
Kerwin (1926)	0·0	8·5	7·5	16·5	0·56
Lawson (1934)	0·0	14·0	10·5	24·5	0·79
Stander and Pastore (1940)	2·7	14·6	13·4	30·7	0·96
Tompkins and Wiehl (1951)	3·0	11·0	10·0	24·0	0·75
Waters (1942)	3·2	8·0	12·0	23·2	0·92
Chesley (1944) (38 papers)	2·5	10·8	11·2	24·0	0·86
Humphreys	0·0	13·71	10·6	24·7	0·80

TABLE II

	Gain 2nd trimester (pounds)	Gain 3rd trimester (pounds)	Total gain (pounds)
Primiparae	13·83 (S.D. 5·65)	11·51 (S.D. 5·65)	22·77 (S.D. 8·44)
Multiparae	13·57 (S.D. 5·77)	9·59 (S.D. 5·53)	23·5 (S.D. 8·33)
All cases	13·71 (S.D. 5·71)	10·6 (S.D. 5·68)	24·7 (S.D. 8·46)

A further breakdown of weight gain into parities illustrates that the mean weight gain in primiparae is 2·27 pounds greater than the mean weight gain in multiparae. As this figure is 4·277 times the standard error of the difference it may be regarded as being statistically significant. This is by no means in accord with the observations of others. Gassner (1862), Kemper (1924a), Kruger (1909), Lorenzen (1922), and Trillat (1928) all record a greater weight gain in multiparae, whereas Beardsley (1941), Hanley (1934), Hannah (1925), Randall (1925) and Zangemeister (1916) record a greater weight gain in primiparae. Bray (1938), Cummings (1934) and Evans (1937) do not feel that there is any statistically significant difference between the mean weight gain in primiparae and multiparae.

Mean Weight Gain per week during the last Trimester

A measure of more practical value than the observation of total weight gain during pregnancy is the rate of gain per week late in pregnancy. As toxaemias usually start late in pregnancy it is important that a normal rate of gain should be established. Accurate rates of weight gain are difficult to record, as most workers, including myself, have not recorded the week to week gain. This means that if one is to assess a mean weekly gain, one assumes that weight is gained at a standard steady rate (if one wishes to apply it to a particular week). This is obviously not so as is shown, for instance, by the ante-partum weight loss, the whole weight gain occurring in less than the trimester. Furthermore, without weekly weight recordings over the course of the last few weeks, one is unable to estimate the standard deviation of weekly gains.

Table I records the mean rate of gain in pounds per week during the last trimester, regardless of parity or age. The rate in the present series conforms fairly closely with the figures of most other authors. It is of interest at this stage to note that Granger (1941) regards a gain of more than 1½ pounds per week in the last trimester as being due to water retention. This, he observes, is one of the earliest signs of toxaemia.

No standard deviation can be calculated, but the standard deviation of the mean gain for the whole of the last trimester is 5·68, from which one can calculate a coefficient of variation of 53·58.

If the coefficient of variation for each week can be regarded as similar to that for the last trimester, the standard deviation is 0·43.

One may summarize, then, by saying that the mean weight gain per week in the last trimester of pregnancy is 0·81 pound (S.D. 0·43). This means that 95·45 per cent of normal cases would have a weekly gain less than 1·66 pounds (more accurately between $0·8 \pm 2$ (0·43)), a fairly close approximation to Granger's figure.

This, however, is rather speculative and could be regarded only as a very rough guide to the expected weekly rate of weight increase in the last trimester of normal pregnancy, if applied to any specific week.

Percentage Maternal Weight Gain

Stander and Pastore (1940) state that throughout the study of their 2,502 cases it was noted that the changes in weight were proportional to the original weight of the patient. On this basis it would seem reasonable that maternal weight gain should be expressed as a percentage of pre-pregnant maternal weight.

	Mean weight gain (pounds)	Mean pre-preg. weight (pounds)	Correlation coefficient	Corr. coeff. / St. error
Primiparae	25·77	123·69	0·075	1·721
	S.D. 8·44	18·26		
Multiparae	23·5	125·02	−0·126	2·74
	S.D. 8·33	19·95		
All cases	24·7	124·32	−0·029	0·9
	S.D. 8·46	19·1		

These figures suggest that in the case of primiparae and when all cases are considered together there is no significant relationship between pre-pregnant maternal weight and maternal weight gain. In the case of multiparae there may, possibly, be some slight inverse relationship between pre-pregnant weight and weight gain, but it is doubtful if it is of real significance.

However, as the weight units used in the measurement of any mass are but arbitrary it is quite reasonable to measure the maternal weight gain as a percentage of pre-pregnant maternal weight. Stander and Pastore (1940) maintain that the maternal weight increase is 24·1 per cent over all cases, and Wodon (1935) gives the gain as about 20 per cent.

The percentage weight gains in this series in primiparae is 21·48 per cent (S.D. 7·1), and in multiparae 19·76 per cent (S.D. 7·75). When all cases are considered together corresponding figures are 20·67 per cent (S.D. 7·46). As the difference in mean gain between primiparae and multiparae is 7·7 times its standard error it may be regarded as being of statistical significance.

When the maternal weight gain, expressed as a percentage of pre-pregnant maternal weight, is related to pre-pregnant maternal weight the correlation coefficients are as follows:

	Correlation coefficient	Corr. coefficient / Standard error
Primiparae	−0·33	9·436
Multiparae	−0·45	9·738
All cases	−0·39	12·39

This demonstrates some small inverse relationship of statistical significance between percentage weight gain and pre-pregnant maternal weight, though this might be expected as one is partially relating the two factors by considering percentage gain before one starts comparing them.

Maternal Weight Gain and Duration of Labour

Not only do many women who gain an excessive amount of weight during pregnancy become the more easy victims of toxaemia, but it has been asserted that they are prone to have more difficult labours (Cummings, 1934; Bingham, 1932; Hannah, 1925; Slemons and Fagan, 1927). To relate maternal weight gain to method of delivery is not a satisfactory means of relating the two factors, as the method of delivery depends on so many diverse factors, e.g., position of placenta and baby, previous obstetric experience of mother, etc. The duration of labour does, however, give us some indication as to the ease, or otherwise, with which delivery

is effected, and has the advantage of being a measurable quantity from which can be calculated a mathematical relationship. It has some of the limitations of calculations involving the method of delivery.

No significant relationship was demonstrated between actual maternal weight gain or percentage maternal weight gain on the one hand and duration of labour on the other when primiparae and multiparae were considered separately, though when all cases were considered together correlation coefficients of 0·0812 and 0·07 respectively were calculated. As the ratios correlation coefficient/standard error were 2·566 and 2·2 there may be some mathematical relationship but it is of doubtful practical value.

Foetal Birth Weight and Duration of Labour

Foetal birth weight was also correlated with duration of labour and no significant relationship could be demonstrated.

Relationship of Foetal Birth Weight to Maternal Weight Gain

To the practising obstetrician a matter of frequent interest is the weight of an expected baby. The mechanical devices of science can give no estimate of the weight of a child *in utero*, and it has been the object of many workers to establish some relationship between factors which can be measured, principally maternal weight gain, and the weight of the foetus at birth. Some workers, notably McIlroy and Rodway (1937), Klein (1946), and Dawson and Borg (1949), fail to demonstrate any relationship between these factors, though none of them estimates a correlation coefficient. Beardsley (1941) and Waters (1942) likewise fail to show any relationship between maternal weight gain and foetal birth weight, though Waters does record heavier babies as being born to women who gain 55-60 pounds during pregnancy. Cummings (1934), Davis (1923), Bingham (1932), Hanley (1934), Slemons and Fagan (1927) and Trillat (1928) all conclude some degree of relationship between their maternal and foetal weight factors. Beilly and Kurland (1945) calculate a correlation coefficient of 0·184928 for maternal weight gain and foetal birth weight, while Kerr (1943), in an outstanding review of 500 normal primiparae records a correlation coefficient of 0·53 between percentage weight gain and infant weight. For actual weight gain and infant weight his correlation coefficient is 0·28.

In the present series correlation coefficients for percentage maternal weight gain and foetal birth weight and actual weight gain and foetal birth weight are shown in the following tables.

Percentage maternal weight gain and foetal birth weight

	Mean birth weight (pounds)	Mean maternal weight gain (per cent)	Corr. coeff.	Corr. coeff. / St. error
Primiparae	7·2	21·48	0·26	5·96
S.D.	0·99	7·1		
Multiparae	7·55	19·76	0·16	3·48
S.D.	1·09	7·75		
All cases	7·37	20·67	0·18	5·69
S.D.	1·05	7·46		

Actual maternal weight gain and foetal birth weight

	Mean birth weight (pounds)	Mean maternal wt. gain (pounds)	Corr. coeff.	Corr. coeff. / St. error
Primiparae	7·2	25·77	0·38	8·7
S.D.	0·99	8·44		
Multiparae	7·55	23·5	0·29	6·314
S.D.	1·09	8·33		
All cases	7·37	24·7	0·31	9·8
S.D.	1·05	8·46		

It is quite apparent from these tables that there is a small but statistically significant relationship between maternal weight gain during pregnancy expressed both as a percentage of pre-pregnant maternal weight and in pounds on the one hand and foetal birth weight on the other.

When percentage maternal weight gain is correlated with foetal birth weight, expressed as a percentage of maternal weight gain, considerable and significant relationship is shown to exist as seen in the following table:

	Mean maternal gain (per cent)	Mean birth wt. (per cent mat. gain)	Corr. coeff.	Corr. coeff. / St. error
Primiparae	21·48	31·96	−0·56	12·82
S.D.	7·1	19·51		
Multiparae	19·76	35·8	−0·65	14·14
S.D.	7·75	16·67		
All cases	20·67	33·78	−0·6	18·97
S.D.	7·46	18·31		

Having established correlation coefficients of statistical significance between the factor of weight gain during pregnancy and the foetal birth weight factor, both expressed in various ways, it remains to calculate regression equations and regression coefficients. As part of the available data in all cases is the parity of the woman, regression coefficients are calculated only for primiparae and multiparae.

Consider, for instance, the simplest example, that of maternal weight gain in pounds and the foetal birth weight, also in pounds. From the data given above one can construct a regression equation for primiparae as follows:

$$\text{Birth weight}-7\cdot2=0\cdot38\times\frac{0\cdot99}{8\cdot44}\times(\text{maternal gain}-25\cdot77)$$

Birth weight—7·2=0·04458, maternal gain—1·149.
Birth weight (pounds)=0·04458, maternal gain (pounds) +6·051.
Regression coefficient=0·04458.

Using a similar technique the regression equation in multiparae for maternal weight gain in pounds and foetal birth weight in pounds (see above) is:

Birth weight (pounds)=0·03795, maternal gain (pounds) +6·6581.
Regression coefficient=0·03795.

If we consider next the relationship between maternal weight gain, expressed as a percentage of pre-pregnant maternal weight, and the foetal birth weight in pounds the regression equations become (see above):

Primiparae. Birth weight (pounds)=0·03624, maternal gain (per cent)+6·4215.
Regression coefficient=0·03624.
Multiparae. Birth weight (pounds)=0·0225, maternal gain (per cent)+7·1054.
Regression coefficient=0·0225.

Lastly we might consider the relationship between maternal weight gain expressed as a percentage of pre-pregnant maternal weight, and foetal birth weight expressed as a percentage of maternal weight gain. The regression equations are:

Primiparae. Birth weight (per cent maternal gain)= −1·538 maternal gain (per cent)+65·01.
Regression coefficient= −1·538.
Multiparae. Birth weight (per cent maternal gain)= −1·398 maternal gain (per cent)+63·43.
Regression coefficient= −1·398.

It is not suggested that when applied to the individual case the use of the regression coefficient gives a standard of change in birth weight for unit change in maternal gain, but it does illustrate a tendency and has been used clinically with results as accurate as any other method of estimation of baby weight, including clinical judgment. Gross errors do, of course, occur in individual cases, even when three regression equations are applied and compared.

The Relationship of Maternal Weight Gain during Pregnancy to Age of Mother

The views of Siddall and Mack (1933), Dawson and Borg (1949), Waters (1942) and McIlroy and Rodway (1937) that young women tend to gain more weight during pregnancy than older ones is supported by this series (see following table).

Wt. gain (pounds) and age (years)	Correlation coefficient	Corr. coeff. / Standard error
Primiparae ..	−0·09	2·05
Multiparae ..	−0·12	2·6
All cases ..	−0·14	4·5

It should be noted that the youngest patient was 14 years old at both conception and delivery, but as she fulfilled all the necessary requirements she was included.

Weight of Infants at Birth

All workers are agreed that boys tend to weigh more at birth than girls (Beardsley, 1941; Beilly and Kurland, 1945; Hanley, 1934; Hannah, 1925; Klein, 1946; McIlroy and Rodway, 1937). The present series covered 1,000

mothers who gave birth to 1,002 babies, 499 boys and 503 girls. The following table shows the frequency distribution of these babies' weights at birth and the results are amplified by the histogram (Fig. 1).

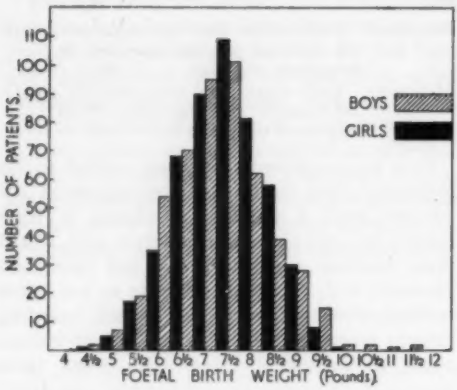

FIG. 1

The Frequency Distribution of Foetal Birth Weight

Birth weight (pounds)	No. of boys	No. of girls	No. of all infants
4 –	0	1	1
4½–	2	5	7
5 –	7	17	24
5½–	19	35	54
6 –	54	68	122
6½–	70	90	160
7 –	95	109	204
7½–	101	81	182
8 –	62	58	120
8½–	39	30	69
9 –	28	8	36
9½–	15	1	16
10 –	2	0	2
10½–	2	0	2
11 –	1	0	1
11½–12	2	0	2
Total	499	503	1,002

Mean birth weight of boys	=7·56 pound
S.D.	=1·09
Mean birth weight of girls	=7·15 pound
S.D.	=0·95
Mean birth weight—all infants	=7·35 pound
S.D.	=1·04

It will be seen that the mean weight of boys at birth is 0·41 pound more than the weight of girls at birth. As this figure is 6·346 times the standard error of the difference we may conclude that the mean weight of boys at birth is more than the mean weight of girls by a statistically significant amount.

Foetal Birth Weight related to Maternal Age and Parity

When considering foetal birth weight in relation to maternal weight gain the following figures were calculated:

Parity	No. of cases	Mean birth wt. (pounds)	S.D.
Primiparae ..	526	7·2	0·99
Multiparae ..	474	7·55	1·09
All cases ..	1,000	7·37	1·05

Multiparae, therefore, produce children whose mean birth weight is 0·35 pound more than the children of primiparae. This figure is unlikely to have arisen by chance as the difference is 5·294 times its standard error.

Having arrived at this conclusion, which seems in harmony with those of others (Bingham, 1932; Hanley, 1934; Hannah, 1925; Klein, 1946), a table was constructed in which the age of the mother and her parity were each considered separately after the pattern of McKeown and Gibson (1951). The resulting figures were suggestive that foetal birth weight increases with parity and is unrelated to the age of the mother when each is considered separately, though more cases in the higher parities would be required to lend this statistical backing.

SUMMARY AND CONCLUSIONS

The mean weight gains and standard deviations in the last two trimesters of normal pregnancy, and in normal pregnancy as a whole, are calculated, and the mean weight gain in primiparae and multiparae compared. The mean weight gain expressed as a percentage of prepregnant maternal weight is also calculated and the gain in primiparae and multiparae are compared. In both instances primiparae are shown to have a higher mean gain than multiparae by a statistically significant amount.

The mean weekly weight gain and standard deviation for the last trimester are calculated speculatively.

It is not possible to demonstrate any really significant relationship between pre-pregnant maternal weight and maternal weight gain during pregnancy, though when maternal weight gain is expressed as a percentage of pre-pregnant maternal weight there is some slight inverse relationship.

The mean duration of labour is correlated with the maternal weight gain in pounds and as a percentage. When all cases are considered together there is some very slight direct relationship of doubtful significance.

Foetal birth weight is also correlated with duration of labour. No significant relationship is demonstrable.

Correlation coefficients, regression equations and regression coefficients are calculated for maternal weight gain and foetal birth weight. The former is variously presented as pounds and as a percentage of pre-pregnant maternal weight. The latter is presented as pounds and as a percentage of maternal weight gain. Significant relationship is demonstrated between the maternal and foetal weight factors in all the combinations.

Correlation coefficients are calculated for maternal weight gain and age of mother. It is shown that younger women gain more weight than older women (when parity is ignored) by a significant amount.

The mean birth weight is calculated for boys, girls, the babies of primiparae, the babies of multiparae and for all babies together. The mean weight of boys is shown to be more at birth than girls by an amount which is unlikely to have arisen by chance. Multiparae are shown to have babies of a heavier mean weight than primiparae. The amount is statistically significant.

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A HISTOCHEMICAL STUDY OF THE HUMAN OVARY

Preliminary Report

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PFLÜGER (1863) was probably the first to differentiate particular types of cell in the ovary apart from those associated purely with the development of the Graafian follicle. He described in detail the interstitial cell of the mammalian ovary, which Bouin (1902) later called the interstitial gland because of the lipoid content of these cells. Reports dealing with the human ovary are few, and deal mainly with the vasculature (Collins *et al.*, 1952; Reynolds, 1950, 1951), or with clinico-pathological conditions (Buxton and Engle, 1950; Laffargue and Luscan, 1951), but quite an extensive literature has appeared dealing primarily with the histochemistry of the interstitial tissue of animal ovaries (Dawson and McCabe, 1951; Hökfelt, 1951; Rennels, 1951; Vincent and Dornfeld, 1948). These authors describe a cell in the ovarian interstitial tissue which appears to contain a large amount of lipoid or lipo-protein, the main feature being a positive reaction to Schiff's reagent. In the course of study of human ovaries, cells with Schiff positive cytoplasm and resembling to some extent the cells described in animal ovaries by these authors, were discovered. The following account deals with the distribution and structure of these cells, and the cytochemical reactions noted with various staining methods.

MATERIALS AND METHODS

A. *Tissue.* Ovaries obtained immediately postmortem from patients who had died in pregnancy or the early puerperium were employed in the first instance. Thereafter, whole ovaries or portions of both ovaries were obtained at operation in non-pregnant patients in the child-bearing age, and in patients at different stages of pregnancy. In all, some 59 specimens were employed: of these, 36 were ovaries of 26 pregnant patients, and 23 were ovaries of 19 non-pregnant patients.

B. *Histological and histochemical techniques.* Some of the specimens were fixed in formol-corrosive, blocked in paraffin, and serial sections cut at 6μ. Others were fixed in formol-saline and serial sections cut on the freezing microtome at 12μ.

Thereafter sections from all specimens were stained by the following techniques, most of which have been described in detail by Pearse (1953).

(i) Haematoxylin and eosin (H. and E.).

(ii) Periodic acid—Schiff (P.A.S.), or simply Schiff reaction.

In addition to this a series of sections was stained by P.A.S., after treating respectively with diastase, hyalase, acetylation, and acetylation with saponification (Hotchkiss, 1948).

(iii) Repetition of the full range of techniques described in (ii) above after treating sections in acetone for 30 minutes at room temperature (Dawson and McCabe, 1951).

(iv) Repetition of the full range of techniques as in (ii) above after treatment in boiling chloroform and methyl alcohol (Pearse, 1951).

(v) Modified Gram stain (McLetchie, 1944).

(vi) Toluidine blue, for metachromasia. A 0·5 per cent solution was employed, and thereafter 2 per cent orange G in saturated aqueous phosphotungstic acid (Pearse, 1952).

(vii) Thionin for metachromasia (Schmorl's method).

(viii) Light green, and also trichloroacetic acid—light green, for the detection of nucleo-protein (Pearse, 1953).

(ix) Sudan IV before and after extraction with warm chloroform.

(x) Coupled tetrazonium, and also benzoylation with the coupled tetrazonium reaction, with, in addition, the coupled tetrazonium technique after performic acid. These were repeated in a few instances after treating for 5-10 minutes in warm chloroform (Danielli, 1947, 1950).

(xi) The Millon reaction.

(xii) Examination for bi-refringency.

The techniques (iii), (iv), (ix), (x), (xi) and (xii) above were employed only on an arbitrary representative number of sections, principally from the tissues obtained at operation.

Results

Sections stained by H. and E. show nothing of significance regarding the cells under consideration. In fact, it is almost impossible to distinguish them from other cells in the granulosa and theca layers of the Graafian follicle, or from cells of the normal ovarian stroma.

P.A.S. Excellent results were obtained by this method and Schiff positive cells are found distributed throughout parts of the ovary, as will be described below. These cells are found to vary in shape, mainly according to situation, from somewhat flattened or spindle-shape, to round and polygonal, with a clear generally centrally placed nucleus.

Developing Graafian Follicle. In the sections studied, Schiff positive cells have not been found in association with primordial follicles. In early developing follicles, however, occasional Schiff positive cells are found in the granulosa layer (Fig. 1). These cells are found also in greater numbers in the granulosa layer of the follicles of fuller development and in which the atrium is formed (Fig. 2). In atretic follicles, where many granulosa cells have become disrupted, amorphous Schiff positive material largely fills the follicle; usually the theca layer is intact, and a few Schiff positive cells are found throughout this layer, extending occasionally into the stroma.

In no instance have these Schiff positive cells been found in the theca layer, except in the case of atretic follicles as noted above. In the granulosa layers these cells are polygonal in shape, and they have a similar appearance in the theca of atretic follicles.

Interstitial Stroma. Schiff positive cells are found in the interstitial stroma, but always in close proximity to follicular structures, such as atretic follicles, corpora lutea, and in particular corpora albicantia (Fig. 3), suggesting an origin thereform. Otherwise they appear to be absent from the general stroma.

Corpus Luteum. Perhaps the greatest concentration of this Schiff positive material is to be found in the corpus luteum, and affords in this situation what would appear to be the most fertile region for examination. The most striking feature is the generalized distribution of strongly positive P.A.S. material in the form of globules. Towards the periphery of the corpus luteum, and also in close proximity to the septa therein, numerous cells containing Schiff positive granules are seen. These appear to be flatter or spindle-shaped towards the periphery, as opposed to the more polygonal shape seen deeper within the corpus luteum. Occasionally areas of fine "peppering" of P.A.S. positive granules are seen, the appearances suggesting dehiscence of the granules from ruptured cells. As mentioned above, Schiff positive material is widely distributed in the corpus luteum in the form of globules of varying size, occurring in groups, not always contained within the confines of cells (Figs. 4 and 5).

In the stroma immediately surrounding older corpora lutea occasional Schiff positive cells are found.

Corpus Albicans. Except in very old corpora albicantia, Schiff positive cells are always present in association with these bodies. Occasionally single cells are found within the substance of the corpus, but the more usual finding is a bi-polar distribution in the stroma in immediate relationship to the hyalinized tissue. In a few instances the Schiff positive cells are found in the stroma surrounding the corpus albicans, but even here there is a tendency to bi-polar distribution.

Frequency. In the ovaries from non-pregnant patients a considerable number of Schiff positive cells are found in the granulosa layer of the developing follicle. In these the material is in the form of a fine granular suspension. On the other hand, in the corpus luteum the material assumes

a globular form, and the number of Schiff positive cells does not appear to be appreciably increased. There are usually, however, many Schiff positive cells in the stroma of the ovary of the non-pregnant patient, but it has not been determined at this stage whether these are related to functioning follicles or merely derived from corpora albicantia. During pregnancy there appears to be a marked increase in the number of Schiff positive cells of both granular and globular forms in the corpus luteum; stromal cells with Schiff positive material seem to be fewer.

In general, all the foregoing observations apply to the ovary of pregnancy, but with the following modifications. In the follicle granulosa the Schiff positive cells appear to be more definitely concentrated towards the atrial border, and the area towards the theca layer is relatively clear, although when compared with the follicle of non-pregnancy it becomes obvious that there is less evidence in toto of the Schiff positive cells. On examining the interstitial stroma it again becomes obvious that there are fewer P.A.S. reacting cells in the ovary of pregnancy, and those which are present are quite definitely in association with some other body, such as the corpus albicans. On the other hand, the corpus luteum of pregnancy shows the strongest concentration of Schiff positive material of any other ovarian body, whether in the pregnant or the non-pregnant state. As this is a preliminary communication, only a rough assessment has been made of these cells regarding their frequency, and modification may be required when fuller studies have been carried out.

The positive reaction to the P.A.S. technique would suggest that the substance may possess a carbohydrate radicle, or a lipoid. Further tests were carried out, and the results follow.

Cytochemistry. According to Rennels (1951) and Dawson and McCabe (1951), the substance in animal ovaries is of lipoid nature, and is removed by acetone, chloroform, etc., and is bi-refringent. In the present study, it is found that, in the sections examined after treating with Sudan, a positive reaction is observed in the material already noted as being Schiff positive. This is particularly noticeable in association with the corpus luteum and the early corpora albicantia, being distributed closely around the latter in a bi-polar fashion, with occasional positive cells within the corpora. Being Sudan positive, it is taken that lipoid is present in the material. However, after treating the section for 5-10 minutes in warm chloroform and then staining with Sudan, it is noted that the reaction is abolished, indicating that the lipoid has been extracted. But neither acetone nor a mixture of equal quantities of boiling chloroform and methyl alcohol abolishes the P.A.S. reaction, therefore the P.A.S. positive material is not identical with the lipoid fraction.

Diastase and hyalase have no influence on the Schiff positive material, indicating that the reaction is not due to polysaccharides.

Throughout the series no evidence of metachromasia could be obtained with toluidine blue or thionin (Schmorl's). This confirms the idea that the substance is not a simple carbohydrate. Nevertheless, the P.A.S. reaction is prevented by acetylation, but is subsequently restored by saponification, and according to McManus and Cason (1950) this means that the material is almost bound to possess a carbohydrate radicle. There is thus some evidence that the substance is probably a mixture of mucoprotein and lipoid.

The coupled tetrazonium reaction gives a weakly positive result in the Schiff positive material, indicating the possible presence of amino acids.

The Millon reaction is negative, therefore tyrosine is absent.

The coupled tetrazonium reaction after performic acid is negative, so that possibly tryptophan may be present. This is confirmed by the reaction being negative after benzoylation. These findings would indicate the presence of protein containing tryptophan.

The modified Gram's reaction reveals the Schiff positive material to be Gram positive, this being most obvious in the globular state in the corpus luteum. Some observers consider this due to nucleo-protein, but in the present series light green before and after extracting with trichloroacetic acid showed no difference in the staining reaction, indicating that the substance is unlikely to be of nucleo-protein nature.

Numerous representative sections were examined under the polarizing microscope without any evidence of bi-refringency.

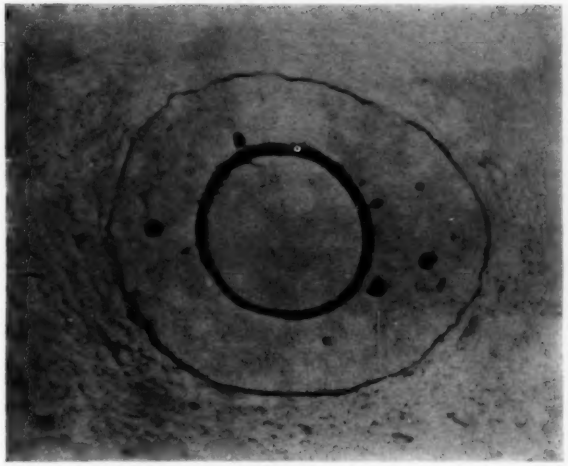

FIG. 1

Section showing early developing follicle with occasional Schiff positive cells in the granulosa layer. The vitelline membrane also gives a strong positive reaction. P.A.S. ×750.

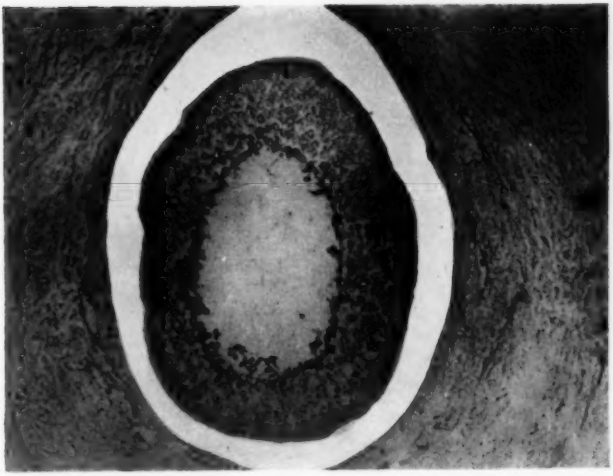

FIG. 2

Section showing follicle with atrium, with Schiff positive cells in the granulosa layer. An indication is obtained also of the distribution. P.A.S. ×280.

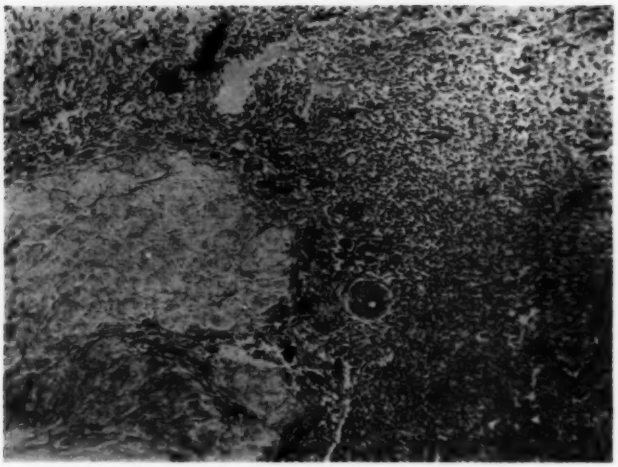

FIG. 3

Section to show Schiff positive cells in the interstitial stroma in close association with one pole of the hyalinized tissue of a corpus albicans. P.A.S. ×200.

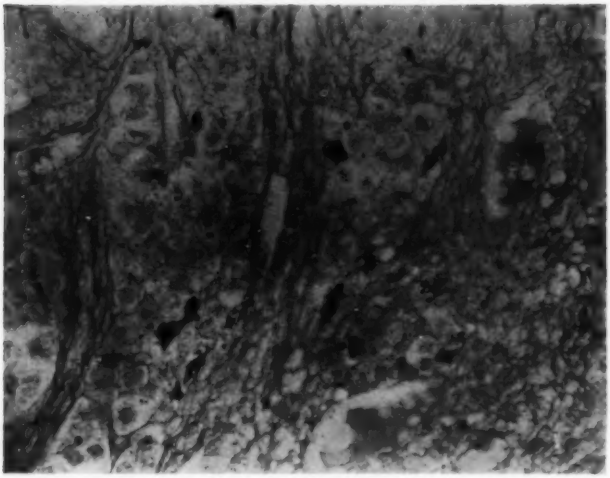

FIG. 4

Section showing Schiff positive cells in the corpus luteum. P.A.S. ×500.

F.H.L.

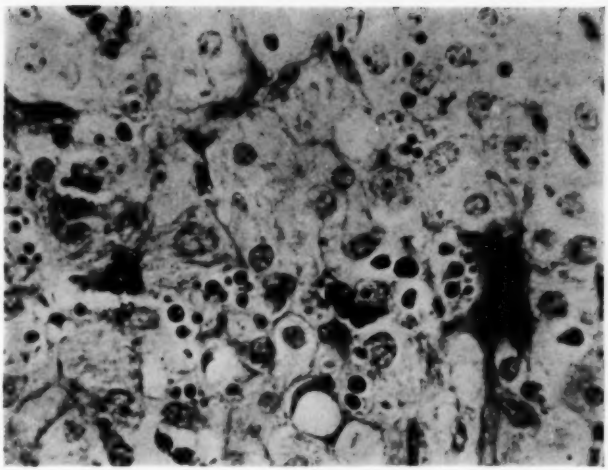

FIG. 5

Section to show globules of Schiff positive material in a corpus luteum. P.A.S. ×750.

To summarize these results, it may be stated that, within the human ovary during the child-bearing period, there is a complex substance, detected histochemically in the form of globules, or granules within cells, present mainly in the corpus luteum, and to a lesser extent in the stroma in close proximity to corpora albicantia, and also in the granulosa layer of the follicles. This substance has the following characteristics. It is Schiff positive and the reaction is not affected by acetone or chloroform/methyl alcohol. Part of the material is sudanophilic but non-bi-refringent: this part is soluble in chloroform. The material or mixture is Gram positive, but does not appear to contain nucleoprotein. It does, however, give reactions indicating the presence of amino acids. It would appear from the results of the various techniques that these cells contain a mixture of lipoid and mucoprotein.

Discussion

In describing his findings in immature rat ovaries, Rennels (1951) has shown that the interstitial tissue possesses intra-cellular bodies which are sudanophilic, Schiff positive, Schultz positive, bi-refringent and acetone soluble. These findings, under similar conditions, have been corroborated by others. In no instance, however, has any attempt been made to determine more specifically the nature of this substance.

From the results given in this paper it is obvious that the mature human ovary contains a substance which, although Schiff positive, in many respects is quite different; this substance although Schiff positive and sudanophilic, is insoluble in acetone, and is non-bi-refringent. It is not the purpose of this present communication to draw any conclusions regarding whether or not these two substances are entirely different as between animal and human tissue, or whether the substance is the same in both instances but in a different form.

It has been shown by Zilliacus (1952a; 1952b) and Zilliacus and Tötterman (1952) that Schiff positive granules and droplets are present in certain pathological cystadenomata in the human ovary. Schiff positive structures, considered by one of these authors (Zilliacus) as being polysaccharide, are present in benign pseudomucinous cystadenoma of the ovary. This author further described this Schiff positive substance in pseudomucinous adenocarcinoma, and notes an inverse ratio between the degree of malignancy and the concentration of the Schiff positive material. From a report by the two authors (Zilliacus and Tötterman) in which is described the P.A.S. staining of Brenner tumours, the positive material in one malignant tumour was scattered all over, and was removed by saliva, which is taken as indicative that the material seems to be glycogen. Apart from these reports it would appear that little research has been made into determining the nature of Schiff positive substances in the human ovary.

As will be seen from the various histochemical techniques employed in the present investigation, part of the purpose of this study has been to rectify this state of affairs and to endeavour to analyze this Schiff positive substance.

The results indicate that there are two substances. As the Sudan reaction is positive this indicates the presence of lipoid, which can be extracted by fat solvents, leaving behind another substance giving a positive reaction with Schiff. This Schiff positive substance, also, is stable when treated with diastase, with hyalase, and after acetylation with saponification; thus indicating that it is not glycogen, although of carbohydrate nature. Further, the positive reaction obtained by the coupled tetrazonium technique indicates that protein is present, and from the correlation of the Millon, coupled tetrazonium, and performic acid reactions this protein is likely to contain tryptophan. Due to the negative results obtained from the light green reaction before and after extraction with trichloroacetic acid, it is unlikely that nucleo-protein is present.

In short, the material under consideration would seem to be a combination of lipoid plus glyco-protein. From the distribution of the cells containing this material it would appear that they are closely associated with the later stages of follicle ripening and formation of the corpus luteum. Pregnancy, with its greatly hypertrophied corpus luteum, seems to increase the frequency of these cells. The significance of these cells is not yet apparent, and further study will be required to determine which of the chemical

fractions, if either, has any physiological activity, or bearing on the physiology of the ovary.

Summary

The presence of Schiff positive material has been described in the rat ovary, but little attempt has been made to determine the full nature of this substance. Equally, reports are few which deal with a like substance in the human ovary.

The material and methods employed in the present investigation have been stated, and it has been shown that the mature human ovary contains a substance distributed in the corpus luteum, but also in the granulosa cells, the corpora albicantia, and the interstitial tissue in close proximity to these structures, this substance being Schiff positive and sudanophilic. The lipoid fraction can be extracted, leaving the Schiff positive material intact. The latter appears to be of muco-protein or glyco-protein nature. Further study indicates that the protein moiety probably contains tryptophan.

I would like to record my appreciation, for his encouragement, to Prof. R. A. Lennie; to Dr. H. Stirling for his interest and the opportunities for obtaining material; and in particular to Dr. A. D. Telford Govan, for his enthusiasm, help and advice throughout this investigation and in the preparation of this paper.

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ABRAHAM CYPRIAN'S OPERATION FOR FULL-TIME TUBAL PREGNANCY IN 1694

BY

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THE following case of tubal pregnancy, remarkable alike for its nature and treatment, is described in an "Epistola" addressed to Thomas Millington, Physician to the King and President of the Royal College of Physicians, upon whom Cyprian had performed lithotomy in 1696. The surgeon from Amsterdam and his patient naturally talked together regarding the cases that had passed through their hands and Millington was so impressed by Cyprian's account of a foetus retained for 21 months that he urged its immediate publication. But pressure of work and Cyprian's illness prevented its appearance till 1700 when it was printed, in Latin text, and published at Leyden.

After a few introductory remarks Cyprian describes his case as follows:

"On the 17th of December, 1694 I was called to Leeuwarden to see the wife of Henri Lewis, a soldier. The woman was 32 years of age and pregnant for the third time in the course of which milk had failed to appear in the breasts while the foetus felt heavier than usual and in position a little lower than in former pregnancies. Violent movements of the foetus and great pain were experienced at the ninth month but no expulsive effort was felt and no sign of amniotic fluid. The child's movements afterwards ceased, the menses returned, and the woman gradually recovered but soon her condition deteriorated and at the 18th month she was obliged to remain abed. She complained of great pain in the region of the umbilicus where subsequently a fungous ulcer appeared. Medical men called in differed in their diagnoses; some thought the foetus was in the uterus, others that it was not, some thought the patient had a hydropsy, others that a growth was present.

"When I had considered the history of the patient," says Cyprian, "I had no hesitation in asserting that she harboured a dead foetus. I compressed the abdomen strongly and felt a great hardness extending to the peritoneum and most marked at the base of the ulcer which, being fungous, easily admitted my little finger to touch what I certainly believed to be the parietal bone of the foetus. I then stated that the dead body was in the right tube and told the patient that if she would permit an opening to be made there was still hope of recovery. She was already so ill that she could not move or take nourishment and was in fact at death's door. The poor woman agreed to anything necessary to rid her of the burden which she had carried for 21 months.

"The patient in her bed was then moved to the middle of the chamber to allow room for those who were to assist me and to ensure that the spectators were able to view the proceedings. Those present who witnessed the operation were Signor Latané and several students from the Academy of Franeker, the First Physician and the Surgeons of the Prince of Nassau, and Mon. Simonides, the patient's surgeon.

"The bed was raised so that I could stand, a position I prefer when performing major operations. Then, having introduced a probe into the ulcer I opened the abdomen on the right side and inserted my index finger, the best of all guides. And when I saw that I had exposed the cavity of the Fallopian tube I put the scissors on my finger and made an incision as long as possible with a single cut which exposed a great part of the foetus. In order to extract it without violence I dilated the opening above and below to about a foot in length while pressing lightly

on the intestines with my left hand to prevent the movement of the diaphragm from pushing them out of the abdomen and thus interfering with the operation. To guard still further against this accident I had placed the patient so that the upper part of the body was a little lower than the rest, a position she maintained afterwards until she had recovered in order to avoid a hernia.

"The head of the foetus now came into view, the feet extending towards the diaphragm. Attached to the Fallopian tube was the placenta which was very thin and the greater part consumed. The cavity was entirely covered with matter resembling pus but looking more closely I found that it was the remainder of the amniotic fluid. There was no ulceration present nor anything the least offensive but care was taken to prevent pus from the ulcerated skin running into the abdomen where it would have caused blood-poisoning and death. I seized the opportunity to demonstrate to my assistants the organs in their natural state; I handled the womb and with pleasure pointed out that as there was no disease of the uterus or of the ovary and left Fallopian tube the patient could certainly again become pregnant if she survived her present ordeal.

"Having withdrawn the foetus a cavity was seen like a very large purse whose wall was so closely connected with the peritoneum that they seemed to be one membrane. To finish the operation I wetted a sponge in warm water and removed all the mucus from within the cavity and then, having well cleansed the wound, I sewed it up with four equidistant stitches by means of a curved needle which passed through peritoneum, muscle and fasciae. A double waxed thread was employed and to reinforce the stitches I applied a slip of wood, covered with linen, on each side of the wound and included them in the sutures but not too tightly. Finally I left an opening at the base of the wound and inserted a tent so that matter flowing out could escape freely. The patient said she had suffered more while the sutures were being inserted than in the operation itself which she had borne without any complaint of severe pain.

"The operation being finished so satisfactorily I prescribed a suitable regimen especially well-sweetened liquid foods. After conferring with Mon. Simonides as to future treatment I left the patient, her mind at ease, in his charge. The woman was visited daily by Mon. Portius, Physician to the Prince of Nassau, while the Princess herself supplied from her own house all the necessary foods. The patient improved day by day and recovered her strength. I often went to see her and noticed that the wound discharged not only from the drainage opening but also between the sutures. The lining of the Fallopian tube separated leaving the external coat joined with the peritoneum at the site of the incision where it became as hard as cartilage. It could easily be seen and touched with the finger while the wound was healing.

"The patient made a perfect recovery and was able to leave her house three months after the operation and since that time she has been healthy and contented. My opinion that she could again become pregnant was confirmed on the 2nd of January 1696, a year after her operation, when she gave birth to a daughter and in the following year to twins, all being normal accouchements. I have preserved the foetus removed from this patient in a liquid balsam in which it was placed over five years ago. It is certainly astonishing that after its long sojourn of 12 months after death in the Fallopian tube the only signs of erosion are on the left side of the head and on one shoulder."

Having finished his account of this extraordinary case Cyprian thought it desirable to pause a little to consider its most important points and to bring forward the reasons of such accidents. He then reviews the anatomy, pathology and surgery of the case step by step and "pauses" to such purpose that his remarks run to 59 closely printed pages of text. To support his views he introduces other cases upon which he had operated including that of a tumour of the parotid as large as a double fist which he had removed in the presence of his father; an interesting case of strangulated hernia —recently published in the *Medical Press*, 20th May, 1953—and a case of hydrocele in which he laid open the whole scrotum to separate the membrane responsible for the water he expected to find. Instead he came upon a thick jelly-like substance similar to that

present in the Fallopian tube of the retained foetus case. He had found such a substance in a ship's captain who, while drunk, had fallen into the hold and injured his head. Nineteen days after the injury Cyprian opened a tumour of the scalp which yielded a mass of this jelly substance but formed of coagulated blood. In these and many other cases he was struck by the fact that no corruption was present and came to the opinion that if one humour remains unmixed with another it does not degenerate into pus.

Cyprian was an advocate of generous incisions in surgery except for the face, neck of the bladder and sphincter ani. Also he was of opinion that wounds of the peritoneum should not be regarded as mortal, and that it was not so dangerous to open the peritoneum as imagined by some surgeons who had too great a fear of haemorrhage.

From the foregoing it will be realized that Cyprian was a worthy son of his father Allardus who was also a noted lithotomist. In this case of retained foetus whose diagnosis had defeated several other surgeons he considered the history and then confidently declared his belief and outlined the steps to be taken to relieve the patient. One must admire the calm manner in which he performed the operation. To gain room for those who were to assist and to allow the spectators a view of the proceedings the bed was moved to the middle of the room and then tilted into a "Trendelenburg" position. When the abdomen was open he was pleased to demonstrate the organs in their natural position, and to prophesy that the woman could again become pregnant. As we picture the scene—Cyprian and his assistants surrounded by students and the medical men doubtless watching with critical eye—it gives the impression of a modern operation and when it is remembered that the woman was conscious throughout it says much for the courage of the patient and proves that Cyprian in his cool and deliberate fashion was entirely master of the situation. The greatest credit is due to this bold and skilful surgeon for his part in setting the patient upon the road to complete recovery.

Biographical Note

Cyprian was born between 1650–60 and became M.D.Utrecht in 1680, his thesis being *Dissertatio de Carie ossium.* He practised in Amsterdam for 12 years and in 1693 was invited to accept the Chair of Anatomy and Surgery at the University of Franeker which he held for only two years. He was pressed to accept a Chair at the University of Leyden but declined the offer and went to London where in 1699 he became a Licentiate of the Royal College of Physicians and a year later a Fellow of the Royal Society. Although a general surgeon he was in most demand as a lithotomist; it is said that in twelve years he performed 1,400 operations for stone and in an historical note on St. Thomas's Hospital by H. B. Robinson it is recorded that "In 1700 the President and some of the Governors were appointed to treat with Doctor Cyprianus, a famous lithotomist from Amsterdam, about instructing 3 chirurgeons for the service of this House in the methods he useth in the operation of cutting for the stone" and this was done, for we find a subsequent note as follows:

"We here take leave to acquaint this Court that the said Dr. Cyprianus at the request of the President was pleased soon afterwards to come over to this Hospital and cutt several persons of the stone (without fee or reward) with very good success, at which Operations the Doctors of this House with Mr. Pepper and severall other surgeons were present." Cyprian was also invited to superintend the extension of the cutting ward where a special surgeon only was permitted to cut for stone. St. Thomas's had a great reputation for lithotomy and probably as the result of increase in the number of patients all the surgeons were performing the operation in 1716. There is an illuminating note on hospital hygiene when fifty years later we read that subscriptions were invited to provide iron bedsteads in the Cutting ward to get rid of the bugs.

Further evidence of Cyprian's fame as a lithotomist is to be found in a letter from Viscount Molesworth to his lady in Dublin.

"1720–1, March 23. Pray send me word how Dublin is now provided with good surgeons in case one should have need of one there, I mean such as are skilled in the difficult operations of cutting for stone, or fistulas, or probing with catheters, which I take to be much out of the

way of common surgeons, and which I think Mr Proby was once well skilled in. Here (since the death of Cyprianus and Salter) there are few or none in high renown left, and those, who have need, go to Paris."

Cyprian had gained the respect of his colleagues in London but was disappointed in the hope of making a brilliant career in England and after a time returned to his home town where he devoted himself particularly to the practice of lithotomy and died on the 26th of April, 1718. Some literary remains attributed to Abraham Cyprian of Amsterdam are in the MSS Department of the British Museum under the pressmark Add 2386–90. It is a collection of recipes in Latin, Dutch and French written in a small and very neat handwriting. A biographical notice, with portrait, by Dr. J. W. Napjus appears as Number XI of a series of papers under the title *De hoogleeraern in de Geneeskunde aan de Hoogeschool en het Athenaeum te Franeker* (*1585–1843*) in the *Nederlandsch Tijdschrift voor Geneeskunde*, 1939. Number XII of the series, June 3, is a reprinting of the retained foetus case with a graphic illustration of the specimen. An earlier notice, by G. P. F. Groshams, was published in the *Nederlandsch Tijdschrift voor Heel-en Verlosk*, Utrecht. 1861–2. Vol. 12, 542–46.

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ELECTROPHORETIC ANALYSIS OF SERUM PROTEINS IN PREGNANCY

A Preliminary Study

BY

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A CONSIDERABLE amount of investigation has been carried out on the protein concentration of the blood in pregnancy, in view of its importance in relation to nutritional disturbances in pregnancy, both maternal and foetal. Most of this work relates to the total protein concentration of the blood and reliable data are available for the variations which occur in normal and in complicated pregnancy. It is obviously an important study in view of the marked protein anabolism which occurs throughout pregnancy. This is partly related to foetal growth and partly to the increase in uterine, placental and breast tissue. In addition there appears to be a storage of protein in the organs in preparation for lactation.

While a certain amount of knowledge has been gained by these studies of total protein levels, they shed little light on the more intimate changes associated with maternal complications of pregnancy such as anaemia, hyperemesis gravidarum, and toxaemia of pregnancy, or on foetal pathology. More recently attention has been turned to the changes in absolute and relative values of the various protein fractions.

Chemical methods, which have hitherto been used in the study of blood protein values, may give rise to fallacies, and more recently electrophoretic analysis of serum proteins has been widely employed in the study of disease states in the non-pregnant subject. Although there are occasional reports of electrophoretic studies of the serum proteins in pregnant patients in the literature, no detailed analysis has so far been undertaken. The position is clearly demonstrated by the fact that the main reference to this subject quoted by Dieckmann (1952) is that of Longsworth *et al.* (1939, 1945). In one of these papers (1939) Longsworth reports, among specimens from patients suffering from various conditions, the results of analysis of a serum from one pregnant individual. In the other communication Longsworth deals with four sera from patients in the post-partum state. It is known that considerable change occurs in these protein fractions in certain diseases particularly in those associated with the liver, kidney and reticulo-endothelial system and, in view of theories currently held regarding the importance of these organs in diseases peculiar to pregnancy, it is surprising to find so little of a factual nature in the literature.

Blood protein values for the non-pregnant individual are not acceptable as normal standards for pregnancy. There is a progressive haemo-dilution in pregnancy and the nitrogen anabolism which occurs may well influence the protein content of the blood. In addition the rate of foetal growth varies throughout the period of gestation and the demands made upon the maternal metabolism must similarly vary. According to Dieckmann (1952) the values for protein fractions obtained by electrophoretic analysis do not differ from those found by chemical methods but this view is subject to some modification in view of his references which are quoted above. By chemical analysis Dieckmann finds that the average serum protein concentration in normal pregnant patients is 6·5 g. per cent and this is 1 g. per cent less than the average serum protein level of 7·5 g. per cent for non-pregnant individuals. A decrease in total serum protein and serum albumin occurs in normal pregnancy. The albumin/globulin ratio

falls from the normal non-pregnant value to a lower value in pregnancy. Dieckmann gives an average value for non-pregnant subjects of 1·6 and an average value in pregnancy of 1·3. He does not attempt to give values for the various globulin fractions. Since pregnancy lasts for a fairly long period and since many of its important complications arise at different stages of pregnancy, normal values for the three trimesters are essential before any reasonable interpretation can be made of the levels found in the abnormalities of pregnancy.

The present investigation is an attempt to establish reliable standard values for serum proteins during the various trimesters of normal pregnancy using the electrophoresis technique.

Material and Methods

Serum was collected from 30 patients, 10 being in each trimester of pregnancy. All patients were healthy women with no sign of oedema and free from albuminuria. The patients' blood pressures were within normal limits, the highest level of normality being taken as 120 mm. systolic and 70 mm. diastolic. The sera were subjected to electrophoresis within 2 hours of collection.

The paper method of electrophoresis was used. The apparatus closely resembles that described by Flynn and de Mayo (1951). A di-ethyl-barbituric acid/sodium barbitone solution of pH 8·6 was used as a buffer. The dishes which contained the anode and cathode carbon electrodes were each half-filled with buffer solution and placed on either side of a central glass rod. The serum for electrophoresis was first submitted for total protein estimations by the Biuret method, and then 0·04 ml. of serum was applied with a micropipette transversely across the middle of a strip of Whatman's electrophoresis paper (3 MM). Each strip of paper measured 12 inches by 5 cm. and a light pencil line drawn across the mid-line of each paper marked the line of application of the serum. The paper, bent at the site of application of the protein, was placed over the central glass rod in the shape of an inverted V. Each end of the paper was immersed in buffer solution, one end being in the anode electrode dish and the other in the cathode-immersing buffer. The buffer solution then soaked each paper by capillary action. A current of 4 milli-amps at a potential of 250 volts was passed from a power pack through the electrodes for 18 hours. Four papers were used each time. After exposure to the current the papers were completely dried on an inclined glass plate placed in a hot air oven. When completely dry the papers were immersed in a staining reagent for exactly 5 minutes. The staining reagent used was 1 per cent Bromophenol blue in 95 per cent ethanol saturated with mercuric chloride. After staining, the strips were thoroughly washed in running water and allowed to dry on a glass plate at room temperature. Each protein molecule possesses acidic and basic groups which cause the molecule to act as a positive ion in acid buffer solution and as a negative ion in alkaline solution. When a current is passed through a paper soaked in alkaline buffer solution the protein molecules will act as negative ions and migrate towards the anode carbon electrode. The rate of migration of each protein fraction varies and we find that the albumin fraction moves farthest from the site of application on the paper whereas the gamma globulin stays close to the application line. Medical science owes much to Tiselius (1937), who may be said to have pioneered protein electrophoresis. Reference to Fig. 1 will show the lines made by the separation of the various fractions. Each protein fraction appears as a blue bar of varying intensity and width across the white of the paper strip. Quantitative analysis was carried out by using a modification of the apparatus described by Griffiths (1952). The paper to be analyzed quantitatively was cleared by immersing it in liquid paraffin and it was then placed between two fine glass plates. The scanning apparatus was set by adjusting the potentiometer until a zero reading was obtained over the undyed area beyond the albumin bar. The glass-enclosed paper was then moved along under the light source and a galvanometer reading was taken. Each 0·1 inch of the paper was similarly assessed for optical density and from the resultant readings a graph was drawn by plotting galvanometer readings against each tenth of an inch of the length of dyed paper. A specimen graph, with the paper from which it was obtained, is reproduced in Fig. 1. Each fraction

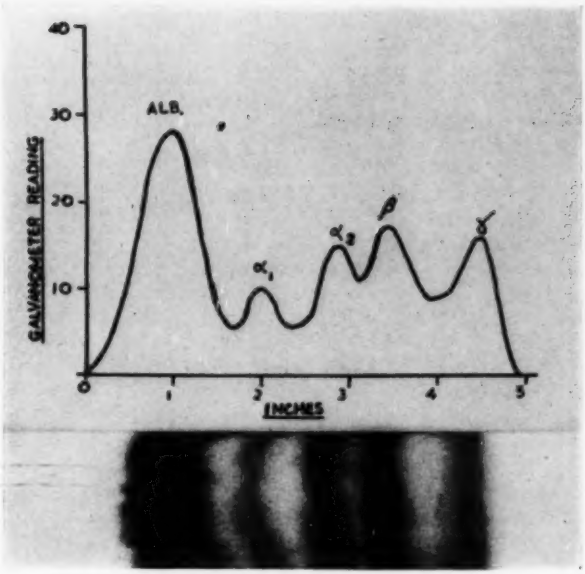

FIG. 1

of the protein complex is represented by a peak or curve in the graph paper. The triangulated area of each fraction peak was estimated thereafter with a planimeter and the amount of protein in each fraction was calculated from the known total protein content of the serum, previously estimated by the "salting out" Biuret method.

In addition to the 30 sera already mentioned a further 5 were obtained from healthy non-pregnant females in the reproductive age-group. All were subjected to analysis by the above technique.

Results

The average values for the normal non-pregnant patients are shown in Table I together with results from normal adults given by several other authors. In the case of Dole and Braun (1944) the figures relate to adult males, 15 in number. Levin *et al.* (1950) do not state the sex and their values relate to a single case only. Dieckmann (1952) gives values for the non-pregnant female, but in this case the estimation of the proteins appears to have been carried out chemically. This is the only reference which we could find in the literature which definitely refers to the non-pregnant female.

From the table it will be seen that our results for total protein agree fairly closely with those of Dieckmann (1952) and Levin *et al.* (1950). Dole and Braun's (1944) figure of 6·38 is very low, particularly for males. According to Bradshaw (1950) who analyzed serum protein values in 2,500 adults the total protein values for the majority of males lie within the range of 7·0 to 7·9 g. per cent, and in females they are slightly higher. Considerable variation exists between the values given by various observers for the individual protein fractions. The value for albumin in our series is reasonably close to that given by Dieckmann and also that reported by Dole and Braun. Levin *et al.* give a very low figure for albumin. Similarly the total amount of globulin in our series is comparable with that reported by Dieckmann. The lower figure quoted by Dole and Braun is a reflection of the abnormally low value which they give for total protein. Levin *et al.* give an abnormally high reading for total globulin due obviously to their low estimate of albumin. These variations are to some extent indicated by the albumin/globulin ratios. Our ratio of 1·5 is similar to that reported by Dieckmann and also that of Dole and Braun. The ratio in the case quoted by Levin *et al.* is abnormally low. Sufficient work has been done to allow us to accept the values for albumin and globulin obtained by chemical methods as accurate. Since our values for these components agree closely with those given by Dieckmann, it seems reasonable to accept the figures we have quoted for the various globulin fractions. It will be noted that they are similar to those quoted by Dole and Braun, being only slightly

TABLE I

Plasma and Serum Protein Values for Normal Adults

Author	Total protein g./100 ml.	Albumin	Total Globulin	α1	α2	β	γ	Alb./Glob. Ratio	Method
				α1+α2					
Levin *et al.* (? single serum) (? sex)	7·02	3·18	3·84	=	1·65	1·17	1·02	0·83	Electrophoresis
Dole and Braun Findings from 15 adult male plasmas	6·38	4·04	2·34	0·31	0·48	0·81	0·74	1·53	Electrophoresis
Dieckmann	7·1	4·4	2·7	No figures given for fractions				1·6	? Chemical
Present investigation—5 adult non-pregnant females	7·1	4·186	2·89	0·358	0·689	0·995	0·848	1·5	Electrophoresis

higher in each instance. As already pointed out, the value given for total protein by these authors is abnormally low and this would be reflected in the absolute figures calculated from the relative values given by electrophoretic analysis.

The average results found in this investigation of serum protein in 30 pregnant women, 10 in each trimester, are shown in Table II. Findings reported by Dieckmann, Longsworth and co-workers (1939, 1945) are recorded.

From Table II it will be seen that there is some difference between the average figures for the various fractions in our series and those quoted by the other authors. Part of this may possibly be due to the fact that we have included sera from patients at several different stages of pregnancy. It must be pointed out, however, before any comparison can be made, that Longsworth *et al.* (1939) refer to 1 case only and Longsworth, Curtis and Pembroke (1945) deal with 4 cases after delivery. Once more, however, there is fair general agreement between our values for total protein, albumin and total globulin and those given by Dieckmann. This provides considerable assurance that our values are reasonably accurate. Dieckmann does not relate the duration of pregnancy to the values he gives and this is obviously necessary before any assessment of results, and the trends they show, can be made. In Table III we have separated the values for individual patients into three groups, in accordance with the particular trimester during which the examination was made.

In the first trimester there is a slight rise in the total serum proteins from the non-pregnant value of 7·1 g. per 100 ml. The rise affects both albumin and globulin but thereafter there is a

TABLE II

Serum Protein Values in Pregnancy

Author	Total protein g./100 ml.	Albumin	Total Globulin	α1	α2	β	γ	Alb./Glob. Ratio	Method
				α1+α2					
Longsworth *et al.* (1939) (? single serum)	6·65	4·29	2·36	=	0·6	1·03	0·73	1·81	Electrophoresis
Dieckmann	6·6	3·7	2·9	No figures given for fractions				1·3	? Chemical
Present investigation—30 pregnancy sera	6·9	3·7	3·21	0·555	0·804	1·102	0·75	1·15	Electrophoresis
Longsworth *et al.* (1945) average of 4 sera (about 1 hour post-partum)	7·83	3·84	3·99	0·46	0·76	1·82	0·95	0·96	Electrophoresis

TABLE III

	Total serum Protein	Albumin	Total Globulin	α1	α2	β	γ	Albumin/Globulin Ratio
Non-pregnant	7·1	4·186	2·89	0·358	0·689	0·995	0·848	1·5
1st trimester Average of 10 sera	7·317	4·328	2·989	0·551	0·622	0·964	0·852	1·4
2nd trimester Average of 10 sera	6·828	3·762	3·066	0·523	0·757	1·027	0·759	1·2
3rd trimester Average of 10 sera	6·48	2·882	3·598	0·592	1·033	1·315	0·658	0·8

progressive fall in the total serum proteins from 7·317 g. through a level of 6·828 g. to 6·48 g. per 100 ml. in the third trimester. The fall in amount of total serum protein represents a drop of 8·8 per cent from the non-pregnant level to the level in the third trimester and a fall of 11·5 per cent from first to third trimester values.

The fall in serum albumin values from early to late pregnancy is approximately 32 per cent and the increase in serum globulin over the same period amounts to 20 per cent.

The fractions of the serum globulin, other than the gamma fraction, increase by varying amounts from early to late pregnancy. α1 increases by 7 per cent, and α2 increases by 66 per cent, and β by 37½ per cent. The gamma fraction decreases by approximately 22 per cent.

The albumin/globulin ratio of 1·5 in the non-pregnant state falls by stages of 1·4 and 1·2 to a value of 0·8 in late pregnancy.

The trends of the various fractions can most clearly be demonstrated by plotting the values in graphic form.

Fig. 2 shows the values of total protein, albumin, globulin and the albumin/globulin ratio in the non-pregnant state and in each trimester of pregnancy. After a slight rise from the non-pregnant state to the first trimester of pregnancy both the total protein and the albumin values show a steady fall. The globulin gradient rises fairly regularly as pregnancy is established and advances towards term. The gradient of the albumin/globulin ratio follows inversely the trend of the serum globulin.

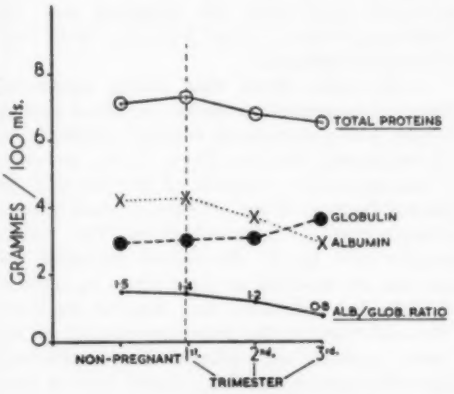

FIG. 2

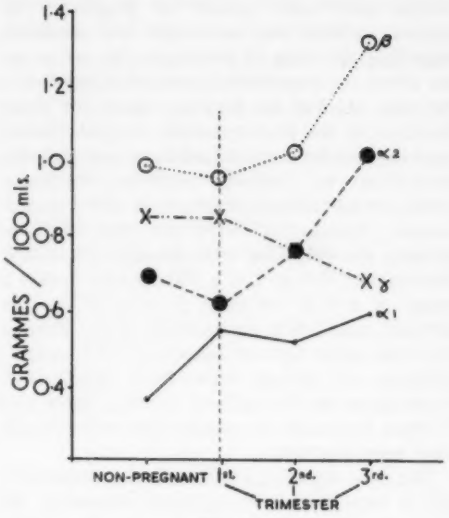

FIG. 3

Graph showing behaviour of Globulin Fractions in Pregnancy.

The graph presented in Fig. 3 shows the values of the globulin fractions before and throughout pregnancy. The α1 fraction shows a slight increase from the non-pregnant value to that in the first trimester, falls slightly in the second trimester and then regains its first trimester value late in pregnancy. The α2 and β fractions form almost parallel curves. After a slight fall in the first trimester they rise progressively, showing their steepest gradient in the third trimester. The γ fraction is unaltered in amount until after the first trimester when it decreases steadily to its late pregnancy value. It is interesting to note that the α and β fractions follow a curve similar to that shown by the total globulins. The γ fraction on the other hand behaves in the same way as albumin.

DISCUSSION

We have been unable to find in the literature any values for the various protein fractions relating definitely to the non-pregnant female.

Values have been quoted for pregnancy by several authors but no details are available regarding the stage of pregnancy. So far as we are aware the present communication represents the first attempt to provide values for these fractions by the electrophoretic method. Values are available for the total albumin and globulin determined by chemical methods. Bradshaw (1950), in an analysis of sera from 300 pregnant women, found that in 90 per cent of these patients the value for total proteins lay within the range of 6·0 to 7·4 g. Dieckmann quotes a figure of 6·6 g. for total protein, 3·7 g. for albumin, and 2·9 g. for globulin. It can be seen from the tables that our figures for total protein, albumin and globulin agree fairly closely with those given by the authors quoted above and it seems reasonable to assume that our methods have been accurate.

The most significant feature is the progressive fall in total protein throughout pregnancy. At first sight this might be thought to be due to the haemodilution which is also a progressive phenomenon during pregnancy, but reference to the values for the various fractions shows that no simple explanation can be offered for this change. If haemodilution were the whole explanation one would expect a fairly equal fall in the values for all the protein fractions. The only fractions, however, which behave in a similar fashion to the values for total proteins, are the albumin and γ globulins. It is apparent, therefore, that the main cause of the reduction in the proteins of the blood in pregnancy is the change in these fractions and obviously albumin is the more important. During the second trimester the $\alpha 1$ component also takes part in the fall in protein values. It is also to be noted that at this period the rising curve for $\alpha 2$ and β is rather flat compared with the third trimester and it may be that during this time haemodilution is an important factor. This is also suggested by the fact that the albumin/globulin ratio alters only slightly in the progress from first to second trimesters. During the third trimester, however, it is apparent that marked changes occur in both albumin and globulin fractions. The albumin shows a more marked fall and there is a steep rise in the $\alpha 2$ and β globulins. There is also a pronounced fall in the γ globulin but the $\alpha 1$ particle shows little change. These alterations are reflected in the albumin/globulin ratio which drops to a very low level.

It is important to establish the values for these protein fractions in the trimesters. Without them it would be impossible to undertake a study of the changes in abnormal pregnancy and even more impossible to compare the findings in disease states in pregnancy with those in diseases of the non-pregnant individual. For example, according to Lewis and Page (1947) malignant hypertension is characterized by a fall in albumin and a pronounced rise in β globulin. This is also characteristic of the third trimester of normal pregnancy and, since hypertensive conditions are common at this period of pregnancy, it is necessary for comparative purposes to know the normal pregnancy levels of these fractions.

No explanation is available at the present moment for the changes in these fractions. Tiselius (1937) has shown that immune bodies migrate with the γ globulins and it is possible that the fall in this fraction during the third trimester is associated in some way with the transfer of immunity to the foetus.

Summary

A study has been made of the electrophoretic pattern of the serum proteins in pregnancy. For this purpose sera from 35 women have been analyzed. Five were not pregnant and the remaining 30 consisted of 3 groups, 10 in each trimester of pregnancy.

It has been shown that during pregnancy there is a progressive decline in the serum protein values. This is due almost entirely to diminution of the albumin fraction. There is also, however, a marked fall in γ globulin. β globulin and the second fraction of the α complex show a continuous rise; $\alpha 1$ scarcely alters. The results suggest that up to the second trimester the changes are modified to some extent by haemodilution but thereafter they become absolute. The variations in the main components of the serum proteins are reflected in the albumin/globulin ratios which fall steadily from a non-pregnant level of 1·5 to 0·8 in the last trimester.

I wish to express my thanks to Dr. A. D. T. Govan, Director of Research, Glasgow Royal Maternity and Women's Hospital, for the great help and encouragement he has given me throughout the preparation of this publication.

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ACUTE SALPINGITIS AND PREGNANCY

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ACUTE salpingitis is considered to be a rare complication of intra-uterine pregnancy. Ectopic pregnancy associated with acute salpingitis has, we believe, never been recorded. We present an instance of each of these conditions.

The cases were seen and operated upon, in the first instance, by the general surgeons at the Whittington Hospital, and after the diagnosis had been established at operation were transferred to the gynaecological department at the hospital. It is interesting that both cases should have presented as general surgical emergencies. We are grateful to our surgical colleagues for allowing us to take over these cases and thank them for permitting us to present them.

CASE REPORTS

Case 1. At 8 p.m. on 3rd September, 1952, Mrs. P.S., a Polish refugee, was admitted to the general wards at the Whittington Hospital as a case of "acute abdomen". There was considerable difficulty in eliciting an accurate history as the patient spoke little English. However, it was established that centralized lower abdominal pain accompanied by vomiting had commenced 24 hours previously. There had been some frequency of micturition and three loose stools had been passed on the day of admission.

One point of this history which was not obtained at the time because of the language difficulties was that insufflation of the Fallopian tubes had been carried out on 25th August, 1952 at the sub-fertility clinic of another hospital. Information obtained from this hospital at a later date revealed that insufflation of the Fallopian tubes had been carried out on 2 occasions. On the first occasion, on the 14th July, 1952, the tubes appeared to be occluded and on the second attempt on 25th August, 1952, there was "patency at high pressure". A biopsy taken on the same date showed a late secretory endometrium.

The patient had been married 5 years without conceiving. She had had a normal period on the 3rd August, 1952. The menstrual history had previously been normal. There was nothing of note in her past medical or family history.

On admission the patient appeared flushed. The tongue was furred. There was generalized tenderness and rigidity over the whole of the lower abdomen, maximal in the right iliac fossa. The release tenderness sign was positive. On rectal examination there was generalized pelvic tenderness. The temperature was 100° F., pulse 96, and respiration rate 20 per minute.

On these findings acute appendicitis was diagnosed and the patient subjected to operation.

The abdomen was opened through a McBurney's incision. The appendix was found to be normal. There was some free pus in the pelvic cavity. Both Fallopian tubes were inflamed and oedematous with free pus issuing from the fimbrial end of each tube.

The patient was seen at this stage by one of us who confirmed the clinical diagnosis of acute salpingitis. The right ovary was enlarged by a follicular cyst to twice the normal size and as it was delivered for inspection a purulent slough separated from its surface. The left ovary was normal. There were no visible tubercles on either Fallopian tube or on the surrounding tissues. A swab of the pus was sent for examination and showed numerous pus cells but culture was sterile.

The appendix was removed and the abdomen closed. Thereafter the patient was treated conservatively as a case of acute salpingitis. Penicillin, 500,000 units twice daily, and streptomycin, g. 1 twice daily, were administered parenterally. Forty-eight hours after operation the temperature was normal and the patient felt well. Steady improvement continued.

On 19th September, 1952, vaginal examination showed a relatively mobile uterus in normal position. There was a cystic, mobile swelling in the right fornix which corresponded in size to the cystic ovary seen at operation. In the left fornix and pouch of Douglas there was a fixed, slightly tender mass of indefinite proportions which was thought to be a tubo-ovarian swelling.

Consecutive weekly erythrocyte sedimentation rate estimations were as follows:

14th September, 1952	..	20 mm. in one hour.
17th September, 1952	..	12 mm. in one hour.
24th September, 1952	..	9 mm. in one hour.

Wassermann, Kahn and gonococcal complement fixation tests on 10th September, 1952, were all negative. An X-ray of the chest was normal.

On 26th September, 1952, the patient had an attack of lower abdominal pain lasting a few minutes which made her feel rather weak. It passed off as quickly as it came and left no residual symptoms. It was not regarded as significant at the time.

On the following 2 days the patient suffered further attacks of colicky abdominal pain which were not so severe as the previous attack on the 26th. On the morning of 29th September, 1952, the patient was seized by yet another attack. This time it was very severe and was accompanied by vomiting. The pain now persisted.

When seen she looked pale and ill. The temperature was 97·6° F., and pulse 74. The abdomen was slightly distended and was acutely tender particularly over the lower region. The release tenderness sign was markedly positive. On vaginal examination there was acute generalized pelvic tenderness with marked excitation pain on moving the cervix. The cervix appeared to be pushed down the vagina. Because of the tenderness the uterus and appendages could not be outlined. There was a dark menstrual-like blood loss *per vaginam* which was the first she had had since 3rd August, 1952. It had started that morning.

The findings at this stage, in conjunction with the late onset of the menstrual period, suggested that the patient was suffering from a ruptured ectopic pregnancy with a pelvic haematocele, and this possibility was discussed, but in view of the inflamed condition of both Fallopian tubes when they were seen at operation 26 days previously a tubal pregnancy in one of them was not thought to be possible. An expectant attitude towards the patient was therefore temporarily adopted.

During the next 6 hours, in spite of a half-hourly pulse chart which showed little variation, it became increasingly obvious that the patient was suffering from a progressive intra-abdominal haemorrhage. In the interim she had developed pain in the left shoulder tip and her respiration rate had markedly increased; she had had 2 slight syncopal attacks initiated by moving her in the bed to facilitate examination and she looked distinctly paler. Laparotomy was therefore decided upon. The blood pressure before operation was 110/70 mm.Hg. A precautionary blood transfusion was started.

The abdomen was opened through a mid-line subumbilical incision. The peritoneal cavity was found to contain much free blood and blood clot. The right Fallopian tube was ruptured at the isthmus and there was a surrounding mass of old blood clot and material suggestive of chorio-decidual products. There was some effusion of blood into the layers of the broad ligament on this side. The left tube was the seat of a pyosalpinx, being distended to the diameter of 2 cm. and tortuously elongated to about 20 cm. in length. The left ovary was attached to the closed fimbrial end and appeared normal.

The ectopic gestation and the right ovary were excised and left salpingectomy was performed. The convalescence of the patient was thereafter uneventful.

Case 2. At 8.30 p.m. on 4th October, 1952, Mrs. E., aged 41, was admitted to the general surgical wards as an abdominal emergency. She had had occasional episodes of abdominal pain in the lower abdomen for several months but these were never severe enough for her to seek medical advice.

Her last menstrual period had been on 12th August, 1952, but she did not think that she was pregnant as she had previously missed periods on occasions. On the day before admission she had vomited her evening meal.

At 9 a.m. on the morning of admission she suddenly developed a central para-umbilical colicky pain which was so severe that she was "writhing on the floor". She felt nauseated but did not vomit. The pain continued intermittently throughout the day, but less severely, and after a few hours became localized to the lower abdomen, particularly towards the right side. The bowels were costive. Micturition was normal. She had had a slight brownish vaginal discharge for about one week before admission.

The patient's past medical and surgical history were normal. There was nothing relevant in her family history. She had 3 normal pregnancies all of which had ended in full-time normal deliveries. Six weeks after the birth of her youngest child 5 years previously she was admitted to the North Middlesex Hospital with vaginal bleeding but was discharged after 3 days. On enquiry from the hospital this episode was thought to have been an abnormally heavy menstrual period. She had had one abortion at 12 weeks between her first and second pregnancies.

On examination the patient looked ill. The breath was foetid and the tongue dry and coated. Abdominal movements were restricted and painful. There was no abdominal distension. Bowel sounds were present and normal. There was marked tenderness and muscle guarding and a rebound tenderness in the right iliac fossa, with some tenderness also on the left side of the lower abdomen. There were no masses felt in the abdomen. The temperature was 99·2° F. and the pulse rate 100. The heart, lungs and central nervous system were normal. On rectal examination there was exquisite tenderness in the pouch of Douglas. No vaginal examination was made.

A diagnosis of acute ruptured appendicitis with pelvic peritonitis was made and the patient subjected to operation. The appendix was approached through a three-inch McBurney's incision which was later enlarged downwards and medially. The appendix was retrocaecal in position and a little fibrin was seen on its surface, but there was no evidence of appendicitis. Appendicectomy was carried out. On passing a finger tip into the pelvic cavity thick yellow pus issued. Inspection and palpation of the pelvic organs showed the uterus to be soft, cystic and enlarged to about the size of a 6-weeks gestation. Both ovaries were normal. The Fallopian tubes were normal in outline but inflamed and oedematous with free pus issuing from their fimbrial ends. One gram of streptomycin was placed in the abdominal cavity and the abdominal wound closed in layers.

The convalescent period was uneventful. The patient was given parenterally penicillin 500,000 units 6-hourly

and streptomycin ½ g. twice daily for 5 days. The temperature on the day following operation was 99° F. but thereafter the patient remained afebrile.

A Friedman test taken 3 days after operation was positive. Vaginal examination on 16th October, 1952, by one of us confirmed the possibility of an intra-uterine pregnancy of about 8-weeks duration. There were now no signs suggestive of salpingitis or peritonitis.

The patient was referred to the antenatal clinic and the pregnancy progressed normally to 17 days past the expected date of confinement. Labour was induced by digital sweep of the membranes from off the lower segment. At 3-finger breadths' dilatation of the cervix the membranes ruptured spontaneously and the liquor was noted to be heavily meconium stained. At this stage also the foetal heart became slow and irregular and, before the situation could be assessed, had become inaudible. The patient was delivered after a labour lasting 15 hours of a stillborn male infant weighing 5 pounds 14 ounces. The cause of death was thought to have been placental insufficiency.

Discussion

In the case of tubal pregnancy presented it is interesting to speculate on the sequence of the various events involved, and on the time relationship of the sowing of the infection in the tubes and of the implantation of the fertilized ovum.

The evidence of ectopic gestation from endometrial biopsy is notoriously unreliable. Novak (1947) in a study of the endometrium in 21 cases of ectopic pregnancy found a decidual reaction in only 7 of them. Also we know it is impossible to distinguish the late secretory phase of the menstrual cycle from the early decidual reaction of pregnancy. The patient could therefore have been already pregnant when the tubes were "insufflated under pressure", ovulation having occurred at or about the 14th day of the menstrual cycle. But it is also possible that she may not have become pregnant until the Fallopian tubes were rendered patent by the second insufflation on the 22nd day of the cycle. In support of the latter, to explain conception at the 22nd day of the cycle, one must assume that an irregular ovulation occurred about this time. This is certainly possible, but its probability may be open to conjecture. Still the coincidence of 5 years infertility suddenly culminating in pregnancy after procedures to render the tubes patent cannot be dismissed lightly.

One assumes that during the act of achieving patency of the Fallopian tubes infection was either implanted in the tube from the cervical canal or vagina, or the procedure reactivated an old latent tubal infection, which was perhaps in the first place responsible for the blockage. We know from experience that acute salpingitis occasionally follows tubal insufflation and its exact aetiology is often questionable. There was no evidence of tuberculosis in these tubes. It may be that the newly fertilized ovum, having gained access to the tube, either became impeded in its course to the uterus by the now increasing oedema of the Fallopian plicae accompanying the infection, or it pocketed in one of the many recesses in the plical folds caused by a previous salpingitis. Infection and nidation must in the first instance have proceeded in unison for a time—that is until the former was arrested by the exhibition of chemotherapy.

The association of salpingitis with intrauterine pregnancy has been described as rare by some authors, notably DeLee (1938) and Lennon (1949), and by others as impossible (Browne, 1946), yet judging by hearsay and after perusal of the literature we would suggest that it is not uncommon. For instance Metzger (1939), a French writer, refers to about 100 collected cases of acute salpingitis in association with early pregnancy. It is, as Lennon points out in 1949 when he presented 2 cases, the English medical literature which is peculiarly devoid of writings on the subject. Lennon makes reference to the French as the only contributors.

With the exception of Lennon's 2 cases which occurred at the sixteenth week of pregnancy all the recorded cases have been associated with pregnancy only in its first trimester.

Of the French writers whose works have been scrutinized, Brindeau (1939), Mocquot (1939), Brocq (1939), Palmer (1939), Bidoire (1939), Devraigne and Ravina (1937) and Fruhinsholz *et al.* (1929) contribute cases which they have personally submitted to operation and describe their findings.

The literature in these cases is not sufficiently complete to allow of an accurate visualization of the underlying provoking pathology nor has the role of the gonococcus as the causative organism been proved in any case so far investigated. In Bidoire's case *Neisseria gonorrhoeae* was isolated from the husband's urethral dis-

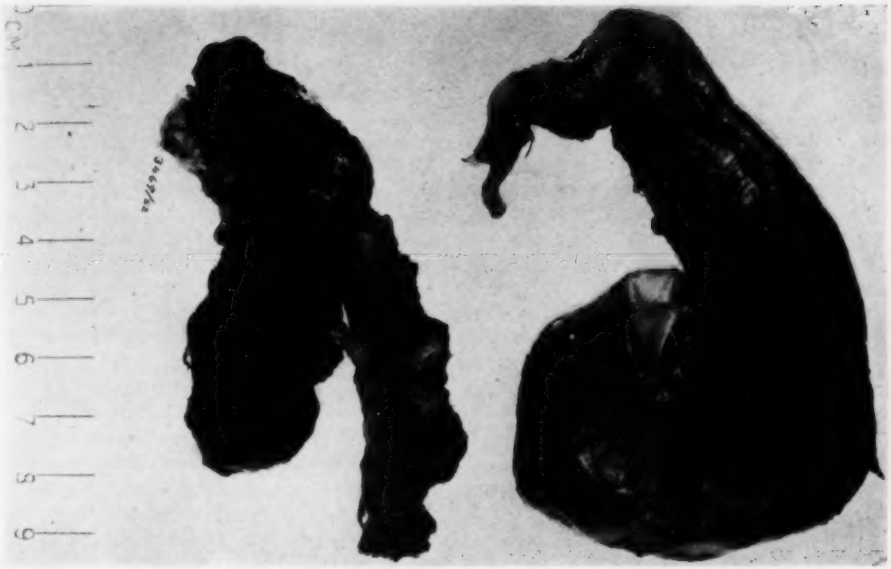

FIG. 1

Two Fallopian tubes, the right very haemorrhagic, 9 cm. long. Near its uterine extremity there is a haemorrhagic swelling, 2·5×3·5×2·5 cm., where the tube is ruptured and filled with blood clot. The left tube, 16 cm. long, is dilated, up to 2·5 cm. in diameter, and filled with inspissated pus. The wall is thickened and fibrotic, up to 0·4 cm. thick.

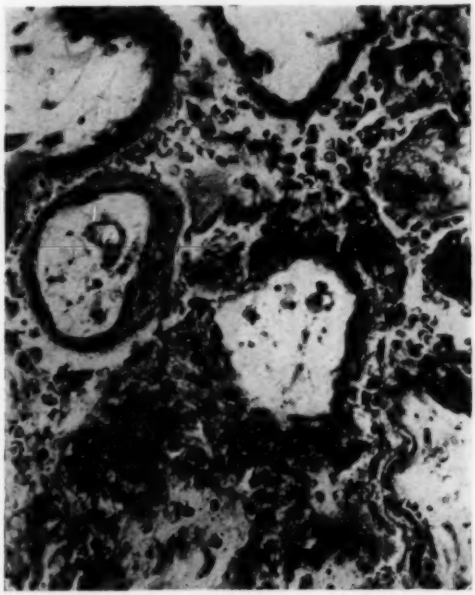

FIG. 2

Chorionic villi and sub-acute inflammatory reaction in Fallopian tube. H. & E. ×330.

charge but not from the patient's cervix or tubes. The predominant organisms found in any of the cases where the tubal contents were submitted to culture were *Bacterium coli* and staphylococci.

Metzger, in discussing the problem of the aetiology of salpingitis in association with early intra-uterine pregnancy, makes the following suggestions as to the possible mode of infection of the Fallopian tubes:

1. The patient contracts the infection at the time of fertilization.
2. She contracts the infection after pregnancy has commenced.

Since we know that the uterus does not become a closed cavity until after the twelfth week of pregnancy this does appear to be possible.

3. During attempts to procure an abortion the intra-uterine infection so produced spreads to the Fallopian tubes.

In Lennon's case signs of infection were found in the products of conception after subsequent abortion suggesting a possible attempt at procuring abortion, although this was denied by the patient.

4. Infection reaches the tube via the blood stream or lymphatics.

We know this is probably the commonest mode of spread in cases of tuberculous infection.

5. From an adjacent focus, for example, the appendix.
6. There is a "flare-up" of an already pre-existing but latent salpingitis.

This possibility would seem to necessitate either—

(*a*) A low-grade infection of the tube in the first instance leaving sufficient patency to permit of the passage of a fertilized ovum and which later, after the nidation of the pregnancy, becomes acute probably because of the congestion produced by the gestation—or—

(*b*) Unilateral salpingitis, the other tube being patent and functioning.

In support of this latter postulate it was noted during survey of the reported cases where the diagnosis of salpingitis had been confirmed at operation that, of the 7 cases presented, 4 of them, those of Palmer, Devraigne and Ravina, Fruhinsholz *et al.* and Mocquot, had a unilateral lesion, and there is sufficient evidence from the description of the pathology to suggest a possible patency of the other tube through which the pregnancy could well have been achieved. Mocquot states definitely that the unaffected tube in his case was patent.

In the case of intra-uterine pregnancy with salpingitis reported above there was nothing in the past history to suggest the possibility of a past tubal infection.

Reports from the North Middlesex Hospital did not aid in this direction. Nor was an interview with the patient's husband any more helpful in establishing a possible gonococcal source of infection. He had never had a urethral discharge.

It is unfortunate that in this case a culture of the effluent from the Fallopian tubes was not taken at operation nor a swab from the cervical secretion post-operatively.

The patient was not aware that she was pregnant and there were no attempts at procuring an abortion. She had had periods of amenorrhoea previously when she visited her native Ireland on holiday and on this present occasion the amenorrhoea appeared to be following pattern. She confessed to having had a vaginal discharge for some days before the onset of symptoms, but as this is a relatively common symptom, particularly in early pregnancy, its presence does not carry much diagnostic importance.

Careful scrutiny of the literature has so far failed to elicit a previously reported case of gestation in the Fallopian tube in the presence of infection of the tube by an organism other than the *Mycobacterium tuberculosis*. It is not difficult to visualize patency of the tubes in mild cases of tuberculous salpingitis where the infection may be isolated to only a few tubercles, and if patency of the tubes is present either intra-uterine or tubal pregnancy can theoretically occur. As regards the *M. tuberculosis* this is borne out in fact. Tubal gestation in the presence of tuberculous salpingitis has been reported a number of times. Kistner, Hertig and Rock (1951) cite 41 cases collected from the literature. Also, according to Donaldson (1952), intra-uterine pregnancy in the presence of tuberculous salpingitis occurs "probably more frequently than we realize".

We have already postulated above that a

previously non-tuberculous infection of the tubes, if it be mild, may leave sufficient patency of the affected tube for a fertilized ovum to pass to the uterus. If the fertilized ovum can reach the uterus then one must assume that, in the past, a number of fertilized ova must have become obstructed in their course down the tube, and yet no cases of their subsequent nidation and growth to rupture, in the presence of active infection, have been recorded. This is difficult to understand. We feel that either (*a*) our premises for assuming patency of the tubes in cases of low-grade infection are incorrect, or (*b*) the mucous membrane of the Fallopian tube has been rendered unsuitable for nidation by the infection, or the infection itself has stunted the growth of the ovum after nidation has occurred, or (*c*) cases of this type have occurred but have not been reported.

To assume patency of the Fallopian tube in the presence of a low-grade salpingitis is justifiable because many cases of pregnancy, after both gonococcal and post-abortional salpingitis, have already been reported in the past, even before the days of chemotherapy and nowadays, since the advent of antibiotics, are common-place.

If the second possibility is correct then it would seem that in the case of ectopic pregnancy antibiotics have changed the picture.

Summary

(1) Two cases are presented, one of ectopic gestation with co-existing pyosalpinx in contralateral Fallopian tubes, and the other of intrauterine pregnancy complicated by bilateral acute non-specific salpingitis.

(2) The literature is surveyed and a case made for considering that acute salpingitis complicating pregnancy occurs more frequently than is believed. The aetiology is discussed.

(3) Co-existing progressive ectopic pregnancy and non-tuberculous acute salpingitis seem to be possible only in this era of antibiotic therapy.

We would like to express our thanks to Dr. Bratton and Dr. Bryson and the staff of the Central Histological Laboratory, The Whittington Hospital, for the photographs and for the preparation and interpretation of the specimens.

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ON THE STRENGTH OF THE FOETAL MEMBRANES

BY

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INTEREST in the problems of premature rupture of the membranes led the writer, some 3 years ago, to endeavour to determine to what extent inherent weakness of the membranes might be concerned in the accident. To this end the strength of the foetal membranes was determined by estimating their resistance to a bursting pressure.

Though differing in detail, the principle of the method was essentially similar to that used by Matthews Duncan (1868) in his oft-quoted classical researches of nearly a century ago. No record could be traced in the literature of repetition of these experiments so that it seemed especially noteworthy to find that the results of the investigation as well as the method closely paralleled those of Matthews Duncan.

The recent paper of Danforth, McElin and States (1953), recording rather similar experiments but with apparently widely differing estimates of the tensile strength of the membranes, was therefore of the greatest interest and prompted publication of the following brief account of the author's research.

METHOD AND MATERIALS

The apparatus used in these experiments is diagrammatically illustrated (Fig. 1). It consisted essentially of a shallow cylindrical chamber (*a*) with open end, connected by suitable tubing through a T-piece to a specially adapted manometer (*b*) and a source of oxygen (*c*). The latter was controlled by a reducing valve permitting the flow of oxygen to be regulated precisely.

The membrane to be examined was placed over the open end of the testing chamber and tied in place with umbilical cord ligature; the grooved circumference of the chamber facilitated this.

Oxygen was introduced slowly to distend the membrane in the form of a "bubble" until it finally burst, the deflection of the membrane being directly measured by means of a counterbalanced lever (*d*). At the moment of bursting the manometer pressure and the height of the "bubble" were recorded.

Mostly rupture occurred near the summit of the "bubble", but when occasionally it began at the circumference of the chamber the experiment was discarded as unsatisfactory, as was any case in which the membrane slipped.

The material consisted of foetal membranes obtained immediately after delivery and im-

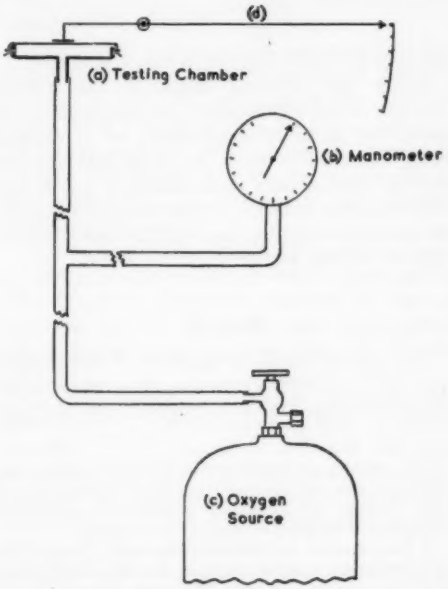

FIG. 1

mersed in normal saline until testing, which was normally within 2 hours.* Initially, some experiments were performed on amnion and chorion individually, but thereafter care was taken not to separate or damage the membranes which were tested together "amnion down".†

Now if P is the pressure at the moment of bursting and R is the radius of "bubble" at the moment of bursting the tensile strength of the membrane T can be calculated by substitution of the appropriate values in Laplace's formula.

$$p=\frac{2T}{R}$$

But Fig. 2 shows that if r is the radius of the cylinder and h is the deflection of the membrane Then $\sqrt{R^2-r^2}+h=R$ so that

$$R^2-r^2=(R-h)^2=R^2-2Rh+h^2$$

$$\therefore\ 2Rh=r^2+h^2 \text{ and}$$

$$R=\frac{r^2+h^2}{2h} \text{ for } h \leqslant r$$

$$\therefore\ T=\frac{PR}{2}=p.\frac{r^2+h^2}{4h} \text{ dynes/cm.}$$

$$=p.\frac{r^2+h^2}{4h}\times 981\times 1{\cdot}37 \text{ dynes/cm.}$$

where p is in mm. Hg, r is in cm., h is in cm.

Using the method described the tensile strength of the membranes was measured in 135 cases, the mean of a minimum of 3 readings being recorded in each. In every case the important clinical data were classified too, in the hope that the strength of the membranes might be correlated with the time and circumstances of rupture of the membranes in labour.

Results

The average tensile strength of 135 membranes was 168900 ± 28800 dynes/cm., the greatest value obtained being 215700 dynes/cm. and the least 92800 dynes/cm. Fig. 3 illustrates the frequency distribution of the data obtained.

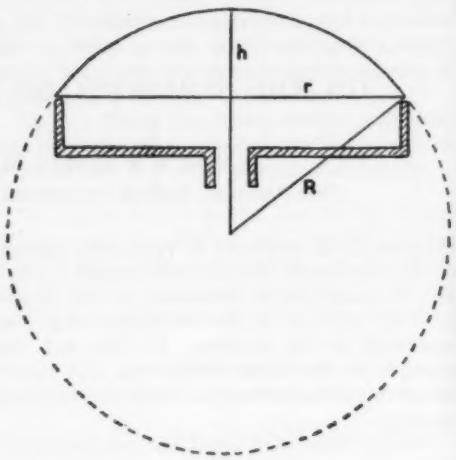

FIG. 2

Danforth, McElin and States express their results using the peculiar and mathematically incorrect standard of "centimetres of mercury per centimetre" and state that the average bursting tension of foetal membranes in their series was 24 cm. Hg/cm. Expressed in the same way, the average tensile strength of membranes in the writer's cases was only 12·6 cm. Hg/cm. —just over half as much.

Attempts to correlate the tensile strength of the membranes with clinical phenomena were not fruitful. The data collected were grouped according to the age and parity of the patient and the duration of the pregnancy, but no signifi-

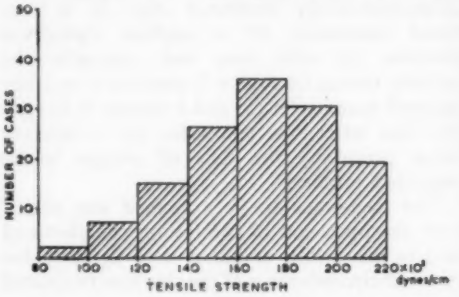

FIG. 3

* It was thought important to test fresh membranes. However, some samples were tested at intervals up to 18 hours without any significant variation in results indicating that immediate testing was not essential.

† Tests showed, as Matthews Duncan discovered, that long before the amnion ruptures, first the decidua and then the chorion give way. The main strength of the membranes lies in the thin but tough and elastic amnion.

cant variation was noted either in the average value of the tensile strength obtained or the frequency distribution of the data.

Depending on their time of rupture and a clinical assessment of the strength of the contractions, the foetal membranes examined were quite arbitrarily classified into three degrees of "clinical strength". It is perhaps not altogether surprising that no significant correlation could be determined between this "clinical strength" and the tensile strength of the membranes. The mean tensile strength in each group showed little variation and the frequency distribution curves showed an over all similarity. The deduction is to be made, therefore, that rupture of the membranes in labour depends on factors other than the tensile strength of the membranes.

The Uterine Force in Labour

The data obtained in these experiments, however, are of interest from another point of view, in that they make possible an estimate of the uterine force transmitted to the foetus during delivery. Indeed it was this problem which mainly concerned Matthews Duncan (1868) in his experiments, and he estimated that the propulsive force applied to the foetal head averaged 16 pounds with a highest figure of 37·58 pounds.*

Now in the experiments described the total force applied to rupture the membranes is represented by $F=p\ \overline{11}\ r^2$ (where p is the pressure and $\overline{11}\ r^2$ the area of membrane exposed to pressure). During labour the area of the head in contact with the pelvic tissues is limited by the occipito-frontal plane, and it is presumed that the lumen of the maternal passage is circular in outline and has a diameter of 10 cm. (4 inches).*

Thus $F=p\times3\cdot14\times5^2=p\times78\cdot6$ dynes (where p is in dynes/cm.^{2})

$=p\times78\cdot6\times981\times1\cdot37$ g. (where p is in mm. Hg)

$=\dfrac{p\times78\cdot6\times981\times1\cdot37}{453\cdot6}$ lb. (where p is in mm. Hg)

The average pressure required to rupture the membranes in the present series was $58\cdot9\pm11\cdot5$ mm. Hg. Applying the above formulae, therefore, the force applied to the membranes was on average 6340 ± 1240 g. wt. or $14\cdot0\pm2\cdot7$ pounds approx. The maximum force obtained was 7500 g. wt. which is equivalent to 16½ pounds approx. Minimum figures were 3230 g. and 7 pounds approx. The conclusion to be drawn is that in normal labour the total uterine thrust transmitted to the foetus usually exceeds that required to rupture the membranes, which is on average 14·0 pounds.

The total uterine force to which the foetus is subjected in labour may be deduced by other means and it is of interest to compare the results of the various methods—as Moir (1936) did.

Thus the intra-uterine pressure may be measured by means of a balloon introduced between the membranes and the uterine wall and connected by a manometer (Bourne and Burn, 1927; Moir, 1934) while more recently the same has been done by directly tapping the amniotic sac abdominally (Alvarez and Caldeyro, 1950) or *per vaginam* (Williams and Stallworthy, 1952).

Moir (1936) found, in average cases, that first stage contractions gave pressures of approximately 60 mm. Hg and using the formula $F=p\,.\,\overline{11}\ r^2$ calculated that the force applied to the foetal head was of the order of 14 pounds. Similar calculations for second stage contractions gave a figure of 24½ pounds with a highest reading of 32 pounds.

Alvarez and Caldeyro (1950) found the intra-uterine pressure in normal labour averaged 35 mm. Hg with occasional readings as high as 100 mm. Hg and Williams and Stallworthy's (1952) figures were not dissimilar (40-90 mm. Hg).

There is reasonable agreement between these figures and it is seen, therefore, that, with due consideration for the many variables, the force required to rupture the membranes is roughly equalled by the force of first stage uterine contractions and is considerably exceeded by that of second stage contractions.

This is perhaps what might be expected but is, as indicated, at variance with the results of Danforth, McElin and States (1953) who cal-

* It is to be noted that in calculating his figures Matthews Duncan assumed the area of head in contact with the pelvic tissues to be 4½ inches in diameter.

culated the tensile strength of the membranes—expressed as cm. Hg/cm.—and found it was approximately double the tension in the membranes at the height of a normal contraction.

The other method of estimating the force of the parturient uterus, by measuring the pull required to extract the foetal head with obstetric forceps, can obviously be no more than an approximation. Matthews Duncan (1868) estimated that a pull not exceeding 80 pounds may be required, while Wylie (1935) quotes an average figure of 35 pounds for primigravidae, mounting to 75 pounds (approximately) in the most difficult cases. As might be expected such figures indicate that the force exerted during instrumental delivery may far exceed that transmitted to the foetus during normal labour.

Summary

(1) A method of measuring the tensile strength of the foetal membranes is described.

(2) The tensile strength of the membranes varies within quite wide limits but is, on average, 168900 ± 28800 dynes/cm.

(3) It is not possible to demonstrate any correlation between the tensile strength of the membranes and the time and circumstances of rupture of the membranes in labour, or other clinical phenomena.

(4) The data obtained enable the total thrust transmitted to the foetal head during parturition to be estimated at an average of 6338 ± 1237 gm. wt. or $14{\cdot}0 \pm 2{\cdot}7$ pounds.

My thanks are due to Professor J. Chassar Moir for permission to publish this paper.

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THE PLACE OF SYMPATHECTOMY IN THE TREATMENT OF YOUNG MARRIED WOMEN

BY

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SINCE sympathectomy has become a recognized treatment for some forms of essential hypertension interest has been aroused among obstetricians concerning the effect of pregnancy on the patient who has had the operation and the effect of the operation on the patient's reproductive capacity. Kellogg (1945), Newell and Smithwick (1947), Austin and Frymire (1948), Peet and Isberg (1949) and Hershenson (1951) have all reported in the American literature cases where pregnancy has followed sympathectomy. In this country Dickson Wright spoke favourably of the operation at the twelfth Congress of Obstetrics in 1949 and Kellar (1950) and Browne (1951) have both referred to its relation to pregnancy. Peet, Isberg and Basset (1948) went a step further when they performed sympathectomy on five cases during pregnancy as an alternative to termination. While four had living children only two had a satisfactory improvement in their hypertensive condition.

Faced with a severely hypertensive patient who is pregnant the obstetrician must consider whether she can be nursed through the pregnancy with the aid of conservative methods of treatment, whether it is advisable to employ sympathectomy or whether the pregnancy should be terminated. If a patient has had a sympathectomy should she risk a pregnancy? If she becomes pregnant after a sympathectomy is it wise to allow the pregnancy to continue? If a woman with a history of stillbirths and abortions undergoes sympathectomy for hypertensive disease can we expect any improvement in her ability to carry a pregnancy? At present the answers to these questions cannot be given statistically owing to the small number of cases on record. It is therefore essential that further cases of this nature should be reported and for this reason the following four histories are of interest.

During the 5 years 1946-1950 inclusive, out of a total of 31,936 deliveries in Ayrshire, 9,023 were conducted in Ayrshire Central Hospital, Irvine (the county obstetrical unit dealing with most of the abnormal cases in the area). Of these 9,023 cases 1,858 had hypertension and these were divided into 1,336 cases of pre-eclampsia and 95 of eclampsia, 369 cases of essential hypertension, 42 of essential hypertension with superadded pre-eclampsia, and 16 cases of chronic nephritis. It will be seen that hypertension constitutes a major problem in this area. In fact the problem is greater than indicated by these figures. For instance cases of pre-eclampsia and essential hypertension if uncomplicated (blood pressure below 160/100 mm. Hg, and no albuminuria) are frequently looked after by their own practitioners at home or in one of the three local maternity homes. The figure for eclampsia, however, is very close to the actual number of cases in the County as almost all are admitted to the Central Hospital as emergencies.

Our first case had a sub-diaphragmatic (Adson type) splanchnicectomy and lumbar ganglionectomy for malignant hypertension while in the Services, and had no previous pregnancies. The other 3 all fell into the small group of 42 cases of essential hypertension with superadded toxaemia. Each of these three had Smithwick transdiaphragmatic splanchnicectomy and dorso-lumbar ganglionectomy.

Case 1. Mrs. G. (Fig. 1). At the age of 25 in May, 1944, this patient developed severe essential hypertension (blood pressure 200/120 mm. Hg), which Professor Learmonth treated by bilateral lumbar sympathectomy with reduction of blood pressure to 135/85 mm. Hg.

Two years later she became pregnant for the first time and attended the antenatal clinic from the sixth month

when the blood pressure was 160/110 mm. Hg. Apart from occasional severe headache and dizzy attacks she was well. At the 38th week she was brought into hospital for a period of rest before labour set in. The day after admission the foetal heart could no longer be heard, the blood pressure rose to 200/125 mm. Hg and a trace of albumen appeared in the urine. Spontaneous delivery of a macerated stillborn foetus weighing 4 pounds 2½ ounces followed a week later. The placenta, which weighed 1½ pounds, showed a white infarct involving 75 per cent of its substance and recent retro-placental haemorrhage. The blood pressure was still high (180/110 mm. Hg) 3 months later.

Just over a year and a half later, in September, 1948, she became pregnant again. The blood pressure was 150/115 mm. Hg at 12 weeks. An uneasy stability was maintained throughout the pregnancy and she was admitted at the 36th week. The blood urea was 42 mg./100 ml. but renal function tests were satisfactory. Caesarean section was carried out at the end of the 37th week and the blood pressure fell to 160/100 mm. Hg. The baby weighed 3 pounds 5 ounces but in spite of careful treatment lived only 13 hours. This placenta weighed 1½ pounds.

This patient has since adopted a child. Her condition now, 9 years after operation and 6 years after the first pregnancy, is poor. She can go about and do her housework but suffers from backache and occasional headache and is easily made breathless. Her blood pressure is 205/130 mm. Hg.

Case 2. Mrs. P., age 22 years (Fig. 2). This patient was admitted in May, 1947, because of threatened abortion in the 18th week of her first pregnancy. Her blood pressure was 200/126 mm. Hg, no albuminuria was present and there was no oedema. The blood urea was 31 mg./100 ml. and haemoglobin 11·5 g./100 ml. The blood pressure settled to 170/110 mm. Hg for 4 weeks then slowly rose to 240/140 mm. Hg. It then fluctuated about the 200/130 mm. Hg level. Albumen appeared in the urine at the 26th week and, as there was no improvement after 3 days, hysterotomy was carried out. Her blood pressure rose to 230/180 mm. Hg during the week after delivery and then settled to 195/120 mm. Hg. A trace of albumen was still present and blood urea was 33 mg./100 ml. on discharge. When re-examined 3 months later her blood pressure was still 200/130 mm. Hg, a trace of albumen was present and she had sub-occipital headache and dimness of vision especially in the left temporal field.

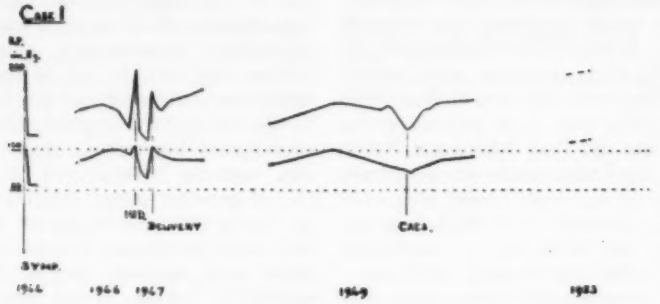

Fig. 1

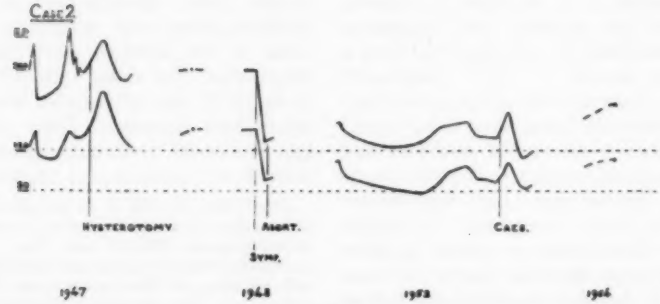

Fig. 2

Medical treatment being ineffective the patient was referred to Mr. Paterson who performed a bilateral, Smithwick type splanchnicectomy with satisfactory reduction in pressure (from 200/140 mm. Hg to 130/90 mm. Hg) and with relief of symptoms.

Abortion at 6 weeks followed the second stage of the operation. On admission to hospital she must have been 1- or 2-weeks pregnant but had not missed a period.

A third pregnancy began 3 years later, in 1951, with blood pressure 145/110 mm. Hg, no albuminuria and blood urea 29 mg./100 ml. The blood pressure fell to 130/90 mm. Hg during most of the pregnancy until the 38th week when it rose to 160/110 mm. Hg but without albuminuria. Lower segment Caesarean section was performed and a live baby weighing 7 pounds 5 ounces delivered. The blood pressure fell after delivery but has risen again and is now stationary at a level of 165/110 mm. Hg. The patient feels well, has no cardiac enlargement and her urine is clear.

Case 3. Mrs. O'R., age 23 years (Fig. 3). This patient was admitted in April, 1948, because of marked hypertension at the 17th week of her first pregnancy. She gave a history of kidney trouble since the age of 5 years, but no convincing evidence of chronic nephritis could be found. There was slight albuminuria but only occasional granular casts. She was able to concentrate her urine to a specific gravity of 1,022 and the blood urea was 31 mg./100 ml. However, the hypertension increased in spite of treatment, she had temporal headache and dimness of vision and termination of her twin pregnancy was therefore carried out at the 19th week, by abdominal hysterotomy. Within a year she was readmitted 9-weeks pregnant. Blood pressure was 184/116 mm. Hg with no albuminuria and no oedema. Blood urea was 34 mg./100 ml. and urine concentrated to specific gravity 1,026. She had been troubled with nausea but not vomiting as much as during the first pregnancy. Headaches also had been a little less severe but there were still eye symptoms. The response to treatment was better and the blood pressure fell to 140/85 mm. Hg, but over the next 2 months climbed slowly to 170/110 mm. Hg. Two weeks later it had risen to 190/125 mm. Hg and when it jumped one night to 206/135 mm. Hg, albumen appeared in the urine. Termination was not accepted until 3 weeks later when the foetal heart had failed. The blood pressure was 275/170 mm. Hg at this time. Again the uterus was evacuated by abdominal hysterotomy. Blood pressure and albuminuria were both reduced quite soon but on discharge after 3 weeks the blood pressure was 160/130 mm. Hg and albumen was present (quarter part Esbach).

Bilateral Smithwick splanchnicectomy was performed a year later in August, 1950, by Mr. Arthur Mackey with a very satisfactory result, the blood pressure being reduced to 125/80 mm. Hg. A third pregnancy began 6 months later. This was normal, the highest blood pressure recorded being 140/95 mm. Hg at the 29th week. She felt some generalized weakness but was free from headache, dizzy turns and breathlessness which had been so troublesome in the previous pregnancies. Because of the 2 previous emergency hysterotomies elective Caesarean section was carried out at term and a healthy female infant weighing 7 pounds 14 ounces delivered. Permission for sterilization was refused. The puerperium was uneventful, the urine being normal. On discharge the blood pressure was 120/76 mm. Hg.

Within 6 months she became pregnant again but did not report until the 22nd week, when blood pressure was 160/110 mm. Hg and marked oedema and albuminuria were present (12 parts Esbach). The blood pressure rose to 220/150 mm. Hg and there were headaches and blurring of vision. The pregnancy was terminated by abdominal hysterotomy, and albuminuria was immediately reduced although the blood pressure fluctuated at the previous high level for a week before subsiding. On discharge this was 160/120 mm. Hg and there was only a trace of albumen. At follow-up 6 weeks and 3 months later she was much as she had been before the operation, with weakness and dizzy turns, headaches and a blood pressure of 200/140 mm. Hg.

Case 4. Mrs. H., age 22 years (Fig. 4). The first pregnancy was apparently normal until the 31st week when the patient was admitted in May, 1946, because hypertension was discovered on the first antenatal clinic examination. Her blood pressure was 150/115 mm. Hg with some oedema of the face, albuminuria (2 parts Esbach) and blood urea 25 mg./100 ml. The urine was concentrating well to specific gravity 1,030. As albuminuria and blood pressure were both increasing in the

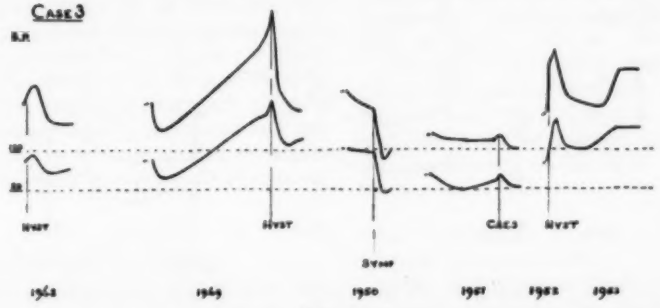

FIG. 3

third week in hospital delivery was accomplished by lower segment Caesarean section. The child weighed 2 pounds and lived only 36 hours. The puerperium was uneventful and on discharge the blood pressure was 155/120 mm. Hg.

A year later she was admitted when 11 weeks pregnant with blood pressure 140/90 mm. Hg and slight albuminuria. While resting in bed the blood pressure rose to 170/100 mm. Hg and albuminuria increased. Therapeutic abortion was therefore induced.

The third pregnancy began in February, 1951. In April she was admitted and termination was considered. The blood pressure was 185/120 mm. Hg, but neither albuminuria nor oedema was present. The blood urea was 17 mg./100 ml.; the urine concentrated well to specific gravity 1,026. The haemoglobin was 12·4 g./100 ml. and plasma proteins were within the normal range. The blood pressure settled to 160/100 mm. Hg and it was decided to try to nurse her through this pregnancy. She was allowed home to rest there from the 16th week until the 32nd week, when a trace of albumen appeared in the urine, and blood pressure was 165/100 mm. Hg. After a week of rest in bed the blood pressure and albuminuria were increasing, so the child was delivered by lower segment Caesarean section. He weighed 4 pounds 5 ounces, but lived only 16 hours. The puerperium was uncomplicated apart from the hypertension which was 200/120 mm. Hg 3 and 4 months after delivery. The patient was advised to consult Mr. Mackey about the advisability of sympathectomy, but did not in fact do so.

She became pregnant for the fourth time on 1st April, 1952, but did not report until June. Her blood pressure was 170/105 mm. Hg and a trace of albumen was present. She was transferred to Mr. Mackey's unit in Glasgow where, after renal and cardiac tests, a bilateral Smithwick operation was carried out. The left kidney was removed at the same time, as calcification, noted in X-ray, was found to be associated with a large abscess cavity in the upper pole. The blood pressure fell to 110/70 mm. Hg and remained low for 4 months. It then rose to 140/100 mm. Hg and fluctuated about this level during November and into December. In the middle of this month the blood pressure reached 160/120 mm. Hg and the patient developed headaches. Lower segment Caesarean section was performed and a child weighing 4 pounds 12½ ounces delivered, which thrived. The puerperium was uneventful and blood pressure on dismissal was 140/110 mm. Hg.

At follow-up she feels well, though easily tired but is able to do her housework and the shopping. Her blood pressure is 140/100 mm. Hg, and she has no albuminuria.

Discussion

Effect of Operation on Hypertension

The natural history of the milder forms of essential hypertension is not clearly understood. The disease appears to be progressive but prognosis is difficult because in many patients the blood pressure remains stationary for long periods and does not produce any effects on the vessels or vital organs. On the other hand the disease may progress more rapidly with resulting renal failure and death from uraemia. Being of short duration and easier to define—marked retinal changes with papilloedema—this phase of malignant hypertension has been more closely studied. Keith, Wagener and Barker (1939) showed that only 21 per cent of cases under medical treatment survived 1 year and only 1 per cent survived 5 years. By comparison, surgical treatment by sympathectomy (Peet and Isberg, 1948), gave a survival rate of 21·6 per cent at 5 years and the majority of these survived 10 years or more (16 per cent). Even among those who did not survive, over two-thirds had some relief from severe symptoms, such as headache, for a time after operation. Comparable figures for the less dangerous phases of the disease have been discussed by Peet and Isberg (1946) and by Smithwick (1948). While statistically sympathectomy produces an improvement

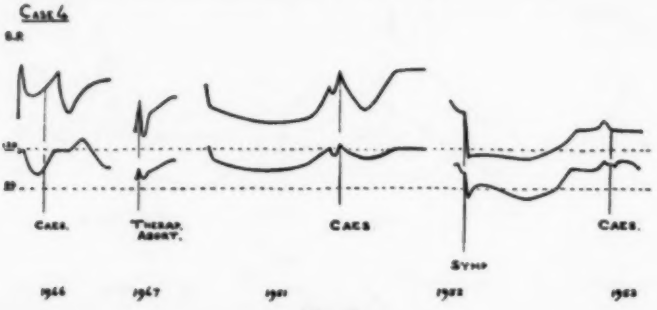

FIG. 4

in survival, in lowering of blood pressure and especially in relief of symptoms yet it is not a very satisfactory treatment. It is a severe operation with a 3 or 4 per cent operative mortality and there are many unpredictable failures (1 in 7). For these reasons many surgeons have restricted its use to severe cases in young people who have failed to respond to medical measures. The development of effective hypertensive drugs has increased this tendency (McMichael, 1952). The disease pursues, on the average, a slower course in women than in men. Women also stand the operation better and have higher 5- and 10-years survival rates.

Effect of Hypertension on Pregnancy

Browne and Dodds (1942) have shown that 60 per cent of hypertensive patients have a rise in blood pressure during pregnancy compared with 7 per cent of normal patients. That is, the chance of developing toxaemia is 8 times greater and the risk of eclampsia correspondingly increased. Concealed accidental haemorrhage is also more frequent.

These complications add greatly to the risk for the foetus and a further danger lies in the degeneration or premature senility of the placenta which was noted first by Wislocki and Dempsey (1946) using histochemical methods and confirmed recently by Clemetson and Churchman (1953) and by Walker and Turnbull (1953). Cox and Chalmers (1953) and Browne and Veall (1953) have also shown that uterine and placental blood flow are reduced in the later months of hypertensive pregnancy, as compared with normal pregnancy.

A second pregnancy may be successful after the first has failed but if two pregnancies are ineffectual the prospect for any future pregnancy is very poor (Theobald, 1953). None of the cases reported had a successful pregnancy prior to operation. In every case hypertension and pre-eclampsia forced us to interrupt the pregnancy before the 33rd week and none of the children survived.

Effect of Pregnancy on Hypertension

This is a very controversial subject. Although the blood pressure may rise in hypertensive cases during pregnancy it is not yet known whether this causes permanent alteration in the underlying hypertensive disease. Barnes and Browne (1945) showed that there is no statistical difference in blood pressure between a group of nulliparous women and a group of parous women. They argue from this that pregnancy cannot be a cause of hypertension. But Chesley *et al.* (1948) following up a large series of pre-eclamptics found that they had significantly higher blood pressure than parous patients who had not had pre-eclampsia. Also he found that since instituting a policy of early interruption of toxaemic pregnancies he had had fewer cases with residual hypertension.

The number of cases of pregnancy prior to sympathectomy does not allow us to make a dogmatic statement. Also the blood pressure before the first pregnancies is not known. In each case there was a rise during pregnancy and a fall after delivery, sometimes delayed. In the end we cannot say that the progress of the disease was more rapid than might be expected considering the youth of these patients, and the severity of their hypertension.

Effect of Normal Pregnancy on the Condition after Sympathectomy

This is illustrated by 3 of our cases, the second pregnancies of Cases 1 and 2, and the third pregnancy of Case 3. Usually the blood pressure remains relatively stationary but occasionally falls in the second 3 months returning to the patient's normal post-operative level about mid-pregnancy. There is a tendency to rise in the last few weeks especially about the 34th or 35th week, but after delivery there is a fall to pre-pregnancy levels or below with slow re-adjustment to former conditions.

This type of pregnancy does not appear to affect the patient's condition after operation. Two of Smithwick's cases and 2 of Peet's cases each had 2 normal pregnancies after operation with no ill effect on the result of their sympathectomies.

Effect of Toxaemic Pregnancy on the Condition after Sympathectomy

If the systolic blood pressure rises more than 30 mm. above the pre-pregnancy level pre-

eclampsia is considered to have supervened. Such a rise is usually associated with oedema, and albuminuria may appear. This picture was found in the first pregnancy in Case 1 and in the fourth pregnancies in Cases 3 and 4. (In Case 4, as sympathectomy was carried out during pregnancy, the blood pressure on discharge from the surgical ward is taken as the base line.) It seems that if this pre-eclampsia continues for any length of time it may lead to permanent aggravation of the hypertension, but if the blood pressure is raised for only a few days no ill effects follow. Prompt termination seems indicated. This was carried out in one of Peet's cases on three separate occasions and the patient regained a relatively normal blood pressure after each pregnancy.

We have been able to follow only 2 of our cases for more than 5 years after operation. Case 1 had a sharp rise of blood pressure at the time the foetus died *in utero*. This was designated pre-eclampsia but lasted only a short time. The second pregnancy was complicated by no such toxaemia. Three years after the second pregnancy her blood pressure has risen 25-45 mm. That is, 9 years after sympathectomy her hypertension is a little worse than before operation. Case 2 had one normal pregnancy after operation (as noted above) and is maintaining satisfactory health after 5 years.

Summary

Four cases of essential hypertension treated by sympathectomy (the last during the fourth month of pregnancy) are described. Each had at least one pregnancy after the operation.

Severe hypertension is associated with grave risks to the mother and foetus. Seven pregnancies before operation produced no surviving children.

Sympathectomy may be performed for the hypertension and if successful reduces these risks of pregnancy and improves the foetal results. After operation 6 pregnancies resulted in a healthy child for all but 1 of the 4 patients. One child died shortly after delivery at the 37th week, 1 died *in utero* at the 38th week and only 1 pregnancy had to be terminated by hysterotomy.

Pregnancy in these cases must be supervised most carefully. Normal pregnancy does not seem to influence the underlying hypertensive condition but if complicated by pre-eclampsia the process appears to be accelerated and the prognosis worsened. Immediate termination may minimize these late effects. On this point more evidence is required.

Other than by the beneficial effects noted above sympathectomy does not influence the course of pregnancy, the type of labour or the mode of delivery. In the cases reported Caesarean section was chosen because of previous emergency hysterotomies or a history of stillbirth. In Smithwick's series 11 of the 14 deliveries were normal and spontaneous.

If in a young woman two pregnancies fail as a result of severe hypertension with pre-eclampsia, sterilization may be advised. Should she resist this course, sympathectomy should be considered as a form of treatment which may both relieve her condition and allow her to have a child of her own.

I should like to thank Professor Sir James Learmonth and Mr. Paterson for their kindness in allowing me to include reports of their cases. I wish to thank also Professor Mackey and Dr. Govan for their help and Dr. de Soldenhoff for his advice and encouragement.

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THE URINARY EXCRETION OF HISTIDINE IN PREGNANCY AND OTHER CONDITIONS

BY

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INTRODUCTION

THE Kapeller-Adler histidine test (Kapeller-Adler, 1933, 1934, 1936) has long been used as a simple guide in the early diagnosis of pregnancy. Urinary histidine output has also been reported to be significantly lowered if pre-eclamptic toxaemia develops (Kapeller-Adler, 1934; Niendorf, 1940; Dawson, 1944). Investigations of this type have been handicapped by lack of a suitable method of estimation of urinary histidine. A simple and precise method has been developed and applied to normal and pregnancy urines.

METHOD

Reagents

(1) 0·880 ammonia, (2) concentrated HCl A.R., (3) 5 per cent suspension of sodium urate in water; allow to stand 24 hours before use and store at 0°, (4) saturated aqueous solution of bromine, (5) amyl acetate, (6) saturated aqueous solution of arsenious oxide in 10 per cent v/v ammonia, (7) saturated solution of potassium carbonate (filtered).

Standards

A suitable "stock standard" is prepared by dissolving 0·25 g. of L-histidine monohydrochloride in 250 ml. of N/10 sulphuric acid. Dilute standards (10 and 20 mg. per cent) are prepared by dilution with water and are put through the same procedure as the test solutions. The results are expressed as mg. per cent of the hydrochloride.

Procedure

To 20 ml. of urine add 0·3 ml. of 0·880 ammonia. Mix by inversion. Filter through a 11 cm. no. 1 paper. Transfer 10 ml. of filtrate to a separatory funnel graduated at 25 ml. Add 1·2 ml. of concentrated HCl and 4·0 ml. of ice-cold sodium urate suspension. Add bromine water until in reasonable excess (starch-iodide paper may be used as an indicator of bromine excess if desired), stopper, and shake to mix. Allow to stand 20 minutes. Remove excess bromine with a few drops of arsenious oxide solution, and make up to the 25 ml. mark with water. Add 20 ml. of amyl acetate. Shake vigorously for at least 1 minute, allow to separate (a few minutes). A small amount of mucoprotein will usually collect at the interface while pigments and chromogenic impurities pass into the organic phase. Filter the aqueous phase (the bottom layer) through a 11 cm. no. 1 paper to remove excess urate and other precipitated material. Add 10 ml. of the filtrate to a centrifuge tube graduated at 15 ml., and make up to the 15 ml. mark with saturated potassium carbonate solution. Mix, allow to stand 10-30 minutes, centrifuge at low speed to clear the solution, and read the red colour in a colorimeter. A suitable instrument is a Hilger Spekker absorptiometer fitted with a green filter (Ilford 604) and cells of 1 cm. diameter.

Collection of Specimens

Single specimens were examined without pre-treatment other than removal of albumen, if present, by boiling. Twenty-four hour urines were preserved with 50 ml. of 2N HCl. The acid was neutralized with 50 ml. of 2N NaOH after collection. A small correction for the complete-

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ness of a specimen was applied on the basis of constant daily creatinine output.

Results

(1) *Pregnancy Urines*

Early morning urines which came into the laboratory for a Friedman test were used. Friedman results and histidine concentration of these urines are compared in Fig. 1. Twelve out of 23 Friedman-positive urines showed a histidine concentration above the normal limit, while only 1 out of 12 Friedman-negative urines showed a raised histidine concentration. In the latter case there was a history of ovarian cyst.

(2) *Other Urines*

The daily excretion of 3 male and 10 female sanatorium patients was estimated over a period of weeks, and the results are shown in Table I. Each individual had a characteristic level of histidine output. This output was unaffected by vitamin dosage and bore no relation to the severity of the disease in tuberculous patients. No characteristic variations in histidine output

TABLE I

Daily Histidine Excretion of 3 male and 10 female patients

Patient	Number of specimens	Mean Histidine content (mg.)	Standard deviation
Mr. A.B. ..	22	220	±39
Mr. T.W. ..	22	200	±35
Mr. J.H. ..	22	104	±19
Miss D.H. ..	38	199	±34
Mrs. M.M. ..	38	204	±38
Miss M.P. ..	38	107	±21
Miss N.C. ..	38	110	±22
Miss G.P. ..	19	110	±41
Mrs. F.M. ..	19	140	±31
Miss P.L. ..	19	180	±42
Miss A.S. ..	19	200	±31
Mrs. R.P. ..	21	97	±24
Miss P.R. ..	21	94	±28

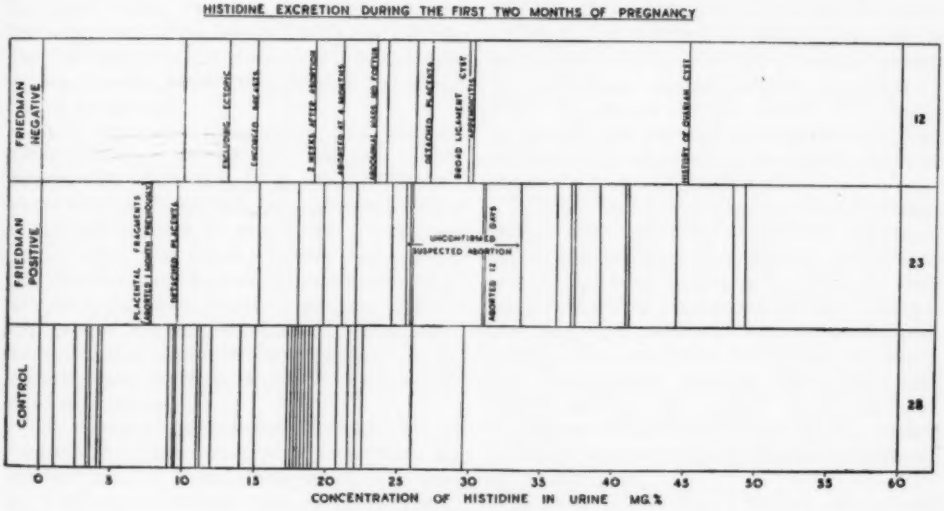

FIG. 1

The *lowest "control" group* shows the range of histidine concentrations in 28 non-pregnant women.
The *middle group* shows the concentrations in 23 women who had a positive Friedman Test; in just over half the cases (12/23) the concentration is above the upper limit of the "control" group.
In the *upper group* of 12 women, investigated for the reasons annotated, the Friedman Test indicated the absence of viable chorionic epithelium; with one exception ("history of ovarian cyst") all the Histidine concentrations fell within the control range.

throughout the menstrual cycle could be detected.

Summary

(1) A precise method for the determination of histidine in urine, depending on a modified Knoop reaction, is described.

(2) There is a characteristic individual level of urinary histidine output.

(3) Friedman results and histidine concentration of early pregnancy urines are compared.

I wish to thank Dr. D. B. Cruickshank for much advice and encouragement and for permission to publish this paper.

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THE SIGNIFICANCE OF HAEMOGLOBIN ESTIMATIONS IN PREGNANCY

BY

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IT is a common practice at many antenatal clinics throughout the country to estimate the haemoglobin of pregnant women with a view to assess iron deficiency, to determine whether some form of iron should be administered, or to appraise the results of so doing.

Varying techniques are adopted for recording the haemoglobin level and there is no universal agreement as to the lower limit of "physiological normality" in pregnancy.

But more important than this, there is considerable obscurity as to what basically we have measured when we state that the woman's haemoglobin is 75 per cent or 11·1 g. per 100 ml., and the reason for this doubt is due to the well-known changes which take place in the blood during pregnancy.

Many observers (Dieckmann and Wegner, 1934; Richter, Meyer and Bennett, 1934; Bethell, 1936; Thomson, K. J., *et al.*, 1938) have shown that the blood and plasma volumes show a decided increase in pregnancy. Dieckmann (1952) states that his and others' findings are that the total amount of circulatory haemoglobin at term is increased about 13 per cent and the total erythrocyte volume is increased 20 per cent. There is thus a relative decrease in haemoglobin concentration in pregnancy and an absolute increase in amount.

This disproportionate increase in plasma to total blood volume during pregnancy makes the interpretation of haemoglobin estimations during pregnancy extremely difficult and complex, and indeed it may truly be said that a haemoglobinometer used in pregnancy is merely portraying the extent of the accompanying "hydraemia".

For some years now haemoglobin readings have been made by myself with the M.R.C. Grey-Wedge photometer at all our antenatal clinics in the Health Division and I had noted the steady fall in haemoglobin values to approximately the 32nd week after which the fall ceased and a slight rise occurred towards term. Magee and Milligan (1951) plotted their results in approximately 2,000 cases and produced a smoothed curve of the 2nd degree parabola type, expressed for the antenatal period as haemoglobin$=100\cdot7-1\cdot0x+0\cdot015x^2\pm6\cdot7$. The decline they showed was from 93 per cent at the 8th week of pregnancy to a minimum of just under 81 per cent from the 32nd to the 34th week.

One is not justified in relating this fall in haemoglobin readings to the iron requirements of the pregnant woman without attempting to assess the reason for this decline. The major reason for the lowered haemoglobin readings as pregnancy advances is the relative increase in plasma over cells, or hydraemia.

The fact has been emphasized by Dieckmann (1952), who advocated using the haemocrit rather than the haemoglobinometer for arriving at a haemoglobin reading, as he found the error associated with a packed cell-volume reading is less than that associated with a haemoglobin reading. The assumption behind this method is that haemoglobin readings and packed cell-volume readings fall together "in unison" and the degree of the lowered haemoglobin reading is a direct measure of the hydraemia as expressed by the haemocrit.

In order to test this, I carried out a small investigation in 216 pregnant women, recording the haemoglobin by the M.R.C. Grey-Wedge photometer, estimating the packed cell volume by the approved method in Wintrobe tubes and then calculating the Mean Cell Haemoglobin (Concentration)—M.C.H.(C.).

The women subject to this investigation were all cases who attended the Lancashire County Council's antenatal clinics in Ashton-under-Lyne, Denton or Droylsden during part of 1952.

Table I shows in columns (1) and (2) the numbers in each of the 7-monthly periods up to term, column 3(a) shows the percentage haemoglobin reading for each group with the standard error and standard deviations in the 2 succeeding columns. Columns 4(a)-4(c) show similar data for the packed cell volume, whilst columns 5(a)-5(c) show the M.C.H.(C.) in a corresponding manner.

It will be noted that the Hb. mean fall reaches its lowest value in the 29th-32nd week, the average level for this month being 77·21 ±1·42 per cent. This level is somewhat lower than the 81 per cent reported by Magee and Milligan (1951), though in my figures cases receiving iron therapy were excluded.

Turning to the packed cell volume, the average range given by Dacie (1950) for non-pregnant women is 36-47 per cent, whilst Dieckmann (1952) gives 37-47 per cent with an average of 42 per cent. My initial reading taken at the 13th-16th week of pregnancy was 39 per cent which fell to its lowest mean figure of 35·12 per cent in the group of 33rd-36th week.

The accompanying graph (plotted on semi-logarithms grid) shows the trend of the Hb., P.C.V. and M.C.H.(C.) percentages from the 13th week until term (Fig. 1).

It brings out clearly the close relationship between the fall of the Hb. and the P.C.V., the haemoglobin percentage following the haemocrit reading very constantly, as Dieckmann has shown.

This again suggests that a record of the women's haemoglobin is giving us (by itself) little information other than the degree of hydraemia which is progressively occurring up to approximately the 32nd week.

If, however, we relate the Haemoglobin and Packed Cell Volumes with each other and calculate the Mean Cell Haemoglobin (Concentration) we arrive at an index which I suggest

TABLE I

Haemoglobin, Packed Cell Volume and Mean Cell Haemoglobin Concentration in Pregnancy

Period of Pregnancy	Number of Cases	Haemoglobin (per cent)			Packed Cell Volume			Mean Cell Haemoglobin (Concentration)		
		Mean	S.E.	S.D.	Mean	S.E.	S.D.	Mean	S.E.	S.D.
1 13th-16th week 196-168 D.	2 13	3(a) 87·08	3(b) ±1·07	3(c) 3·86	4(a) 39·0	4(b) ±0·54	4(c) 1·93	5(a) 33·1	5(b) ±0·41	5(c) 1·48
17th-20th week 168-140 D.	20	84·8	±1·78	8·38	38·7	±0·54	2·54	32·4	±0·44	2·05
21st-25th week 140-112 D.	34	84·29	±1·43	8·30	37·76	±0·50	2·94	33·03	±0·28	1·60
26th-28th week 112-84 D.	42	81·88	±1·28	8·34	37·05	±0·42	2·7	32·8	±0·33	2·12
29th-32nd week 84-56 D.	41	77·21	±1·42	9·1	35·22	±0·48	3·1	32·48	±0·42	2·70
33rd-36th week 56-28 D.	49	77·49	±1·08	7·6	35·12	±0·46	3·2	32·85	±0·25	1·73
37th-40th week 28-Term	17	78·41	±1·77	7·28	35·41	±0·88	3·6	32·6	±0·68	2·8
Total	216									

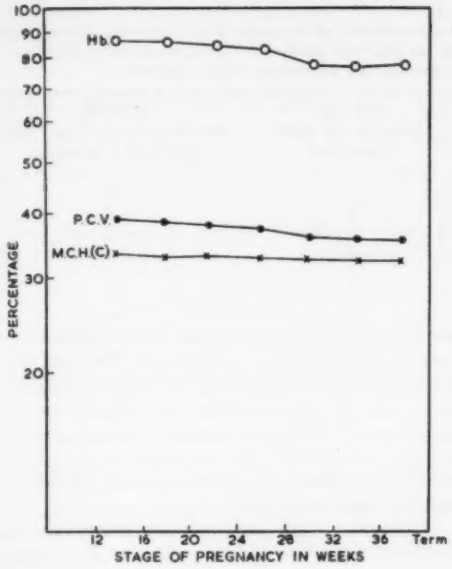

FIG. 1

Trends of Haemoglobin, Packed Cell Volume and Mean Cell Haemoglobin Concentration.

is the only reliable index of iron sufficiency in pregnancy.

Whitby and Britton (1953) state that "the M.C.H.(C.) is the true indication of the presence or absence of iron deficiency; it is the key to iron therapy".

The Mean Cell Haemoglobin (Concentration) stands firm amidst the welter of fluid changes which beset the pregnant woman and which give rise to fluctuations in the Hb. and P.C.V. percentage figures, which are unrelated to the basic haemoglobin content of the cells.

Referring to Table I it will be noted that there is very little variation in the M.C.H.(C.) between one month and another, as pregnancy proceeds; the graph with its comparatively horizontal line illustrates this point. The actual value during these 7 months lies between 32 and 33 per cent.

If we take the mean and standard deviation for the overall average M.C.H.(C.) to be 32·7 and 2·0 respectively we arrive at an arbitrary lower limit of 30·7 (1.S.D. below the mean) which we may assume to be the datum line below which some degree of anaemia exists.

Some line of demarcation must be applied to the M.C.H.(C.) readings to separate low from medium and high values and the 1.S.D. level below the mean will (if the distribution is symmetrical) cut off approximately the lowest 16 per cent of the total values.

It is interesting to compare the working of the two criteria of anaemia as thus defined, viz.:

(1) The 70 per cent and below haemoglobin reading.
(2) The 30·7 per cent and below M.C.H.(C.) reading.

Table II illustrates the application of the above two "standards of anaemia" to the 216 cases in the series.

Thirty-six cases were found to have a Hb. reading of 70 per cent or below and in only 18 or half of them was the M.C.H.(C.) showing "anaemia".

Thirty cases were found to be anaemic on the M.C.H.(C.) arbitrary standard (1.S.D. below mean) but only 18 of these were also found to be anaemic by the other standard.

It is clear from this table that the two indices under test are telling different stories and we must make up our mind which is the "relevant" one for our purpose, viz., to evaluate the pregnant mothers' iron requirements.

It will be noted in this connexion that the straight Hb. percentage tends to select more "anaemic" cases as we approach the 32nd week and, whilst this is also true to some extent of the M.C.H.(C.), it is not so marked a feature. This differential selection on the phase of pregnancy is no doubt a hydraemic manifestation in the former case.

The haemoglobin percentage index says that there is a reduced amount of haemoglobin per unit volume of blood, the M.C.H.(C.) says that the erythrocytes are not to blame for this because there is substantially the same index early as in late pregnancy (viz., 32-33 M.C.H.(C.)); the cause, therefore, of the haemoglobin percentage reduction is a dilution phenomenon. It might be argued that the quantity of haemoglobin per unit volume of blood is a practical index, and indeed it would be if the total blood volume remained constant in pregnancy, but as noted

TABLE II

Showing the number of cases out of 216 pregnant women found to be anaemic on the standard of 70 per cent Haemoglobin or below (Column 2) and the number found to be anaemic on the arbitrary standard of 30·7 per cent M.C.H.(C.) (Column 4). Column 3 shows the number of cases who are anaemic by both standards

(Col. 1) Period of Pregnancy	(Col. 2) Anaemic on 70 per cent Haemoglobin Standard	(Col. 3) Anaemic on both Standards	(Col. 4) Anaemic on 30·7 per cent M.C.H.(C.) Standard
13th-16th week ..	0	0	2
17th-20th week ..	1	1	3
21st-24th week ..	1	1	2
25th-28th week ..	6	3	6
29th-32nd week ..	12	7	7
33rd-36th week ..	12	3	6
37th-40th week ..	4	3	4
Total ..	36	18	30
Percentage of Total number of cases (216)	17	8	14

above it is increased by about 20 per cent and the relative quantities of plasma and cells are disturbed. Unless, therefore, we have a method of showing the increment in total blood volume our haemoglobin percentage index is not a true index of haemoglobin deficiency.

The M.C.H.(C.) therefore remains the reliable index of "anaemia" in pregnancy, if this condition exists at all.

SUMMARY AND CONCLUSION

An analysis of the blood of 216 pregnant women at different months of pregnancy confirms the fall in the haemoglobin reading which occurs until approximately the 32nd week with a subsequent slight rise to term.

It further shows the parallel fall in the packed cell volume.

It shows comparatively little disturbance in the mean cell haemoglobin concentration throughout the pregnant period.

It is submitted that the first two findings are an expression of the hydraemia of pregnancy and that they have little significance as a measure of the iron requirements of the pregnant woman until such time as we can measure simply the total increment in blood volume which is occurring in pregnancy.

The mean cell haemoglobin concentration, however, which ranged from 32·4 to 33·1 (comparatively little variation), shows no significant trend downwards as pregnancy moves towards term. This index is the true index of the iron requirements of the pregnant woman.

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THE MECHANICS OF THE UTERUS IN THE FIRST STAGE OF LABOUR

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ABSTRACT

A THEORETICAL discussion is given of the mechanical forces which, on the basis of physical principles, may be considered to be operating in the wall of the uterus during the first stage of labour. It is shown that it is a reasonable postulate to suppose that during an efficient labour all the muscle fibres in the uterus wall are contracting at maximum efficiency and that there is no need to invoke a gradient of activity to explain progressive labour.

INTRODUCTION

The general obstetrical picture of the uterus given in the medical schools is that it is a bag which, apart from the modifications caused by the insertion of the Fallopian tubes, has roughly the shape of an egg, though the fundal segment of the uterus, compared with its lower segment, is of rather larger dimensions than the upper segment of an egg compared with its lower segment. The walls of this uterus are composed of (*a*) contractile tissue, (*b*) elastic tissue. The contractile tissue is arranged in three main groups: the first runs from the cervix up towards the fundus and sweeps round the Fallopian tubes; the second runs round the uterus, ascending in a clockwise spiral until the fibres blend with the first group around the Fallopian tubes; the third group of contractile fibres is similar to the second group except that the spiral is anticlockwise.

When the activity or function of this contractile bag is discussed, the classical obstetrical picture is of a thick fundal segment exerting a large force which overcomes a thin lower segment, thus drawing the myometrium upwards towards the fundus which thickens further, and leaving the lower segment so that the cervical os is distended, in this way producing dilatation of the os and final advance of the foetal head.

This picture, however, is a qualitative one and to a certain extent bears no relation to the mechanical factors which must be satisfied if the uterus, whose action must satisfy mechanical principles, is to perform effectively.

MECHANICAL ANALYSIS

A way of studying the action of the uterine muscles would seem to be to consider the shape of the uterus during a contraction and to argue back towards the forces which are responsible for the shape. We therefore start by imagining the uterine wall to consist of a matrix of units, each of which is made up of a contractile element "A" (i.e., a contracting machine capable of being put into or out of gear through the chemical processes in the tissue) in series with an elastic element "B", the two being paralleled by another elastic element "C" (Fig. 1). There is a basis for this picture in the work of Hill (1949, 1950), Levin and Wyman (1927) and others on the contractions of skeletal muscle and

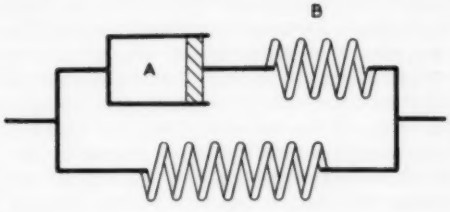

FIG. 1
A muscle unit.

the heat produced during these contractions. These units must be thought of as microscopic, and the groups of contractile strips, mentioned in the introduction, must consist of large numbers of these units in series.

The uterus then becomes a balloon which has one property which balloons do not have, the property of active contraction. In a balloon, if the internal pressure is increased the balloon expands, and, due to the elasticity of the material of the wall, the internal stress in the wall increases so that at all times the pressure exerted on the fluid in the balloon by the wall is equal to the pressure of the fluid upon the wall of the balloon. If the elasticity of the balloon is not uniform throughout the wall, the expansion is greater in any place, where the elasticity is lower than over the rest of the wall, and so the shape of the balloon changes. In the uterus the contractile elements of the uterine wall actively contract (the engine is put into gear), causing all the elastic elements in series with them to stretch. Thus the internal stress in the uterine wall rises and so the pressure within the uterus itself rises although the volume does not change, for the increase in length of the elastic elements is equal to the decrease in length of the contractile elements. If, however, the contractile elements in one portion of the uterine wall were not to become active, we know, from the physiological experiments already cited, that the contractile elements will "give" without exerting any force and the elastic elements in series with them will therefore have no force applied to them. That section of the uterine wall will therefore behave as a purely elastic membrane, the elasticity being due only to the parallel elastic members, the third component of the muscle unit. It therefore follows that, in order to produce a force which will be in equilibrium with the force produced by the contracting portion of the uterine wall, the inactive portion will stretch and balloon outwards, thus changing the shape of the uterus in the same way as a balloon with a weak portion will become distorted. Should, however, the portion of the uterine wall not be entirely inactive but only *less* active than the rest of the wall, then the same sort of distortion will take place only to a lesser degree. This line of argument is strikingly illustrated in a paper by Rudolph and Ivy (1931) in which they describe a uterus which at each contraction produced a cyst in the upper left portion of the patient's abdomen. This round bulge was soft and the foetal breech could be felt through it, a condition which is not observed during a uterine contraction. Rudolph and Ivy postulate that one side of the uterus was not irritable and so did not contract. When the contraction of the uterus as a whole had subsided the cyst disappeared and the uterus was found once again in the mid-line position, as the elastic elements of the muscle units contracted when the interior pressure was removed.

This case shows that a reduction of activity in one part of the uterus caused marked distortion of the uterus and was associated with a long first stage and dystocia.

Let us now look a little more precisely at the muscular forces which must be operative in the uterine wall. The first postulate we make is that during the first stage of labour the uterine wall is acting upon a volume of water. The foetus is floating in water and everywhere between the foetus and the uterine wall there is a water layer. Under such circumstances we can speak of "pressure" within the uterus and this pressure must everywhere be the same, because a fluid transmits pressure unchanged. In any experiments in which probe balloons with transmitting tubes have been introduced into the uterus between the uterine wall and the amniotic sac, and the pressures recorded from different parts of the uterus have not been the same, the conditions cannot have been as described above. The cause of unequal pressure may have been that pressure was not actually being measured, as for example when the balloon is placed in the os of the uterus which, being open to the atmosphere, cannot have a pressure other than atmospheric, or (2) that an abnormality had occurred, such as a contraction ring. Such a ring is capable of pulling the mid-segment of the uterine wall tightly against the foetus and dividing the uterine cavity into two compartments, in each of which the pressure will be everywhere the same though the pressure in one compartment may be different from that in the other compartment.

The second postulate we make is that there

are no gross changes in the shape of the uterus during the first stage of labour. The cervix is dilating but, from the junction of the cervical tissue with that of the lower segment, up to the fundus, the uterus is remaining the same shape. Clinical observations on cases of unobstructed labour with a minimum discomfort and distress to both mother and foetus indicate that this is so and the tokodynamometer experiments of Reynolds *et al.* (1948a, 1948b) and of Delson *et al.* (1950) have been interpreted by Halliday and Heyns (1952) as implying a hardening of the uterus accompanied by its rotation forward in the abdomen without gross change of shape.

Calculation of Forces

To calculate the internal stresses in the uterine wall upon the basis of physical principles it is necessary to assume some geometrical shape for the uterus to which mathematical formulations of physical principles will apply without producing insoluble equations. A possible approximation to the actual shape might be described as follows (see Fig. 2). A section through the uterus shows an upper portion which is circular in shape with a radius of curvature R_1 and a lower portion which is also circular in shape with a radius of curvature R_2. The upper and lower portions are joined by a conical mid-section. The three dimensional shape of the uterus is obtained by rotating this figure about its long axis AB. In actuality the mid-section of the uterus is slightly curved outwards as shown in dotted lines and, as the uterus is slightly flattened from front to back compared with its dimensions from left to right, a simple rotation of the figure about the vertical axis does not give the true shape, but the deviations from actuality will not violently affect the magnitudes to be obtained in what follows.

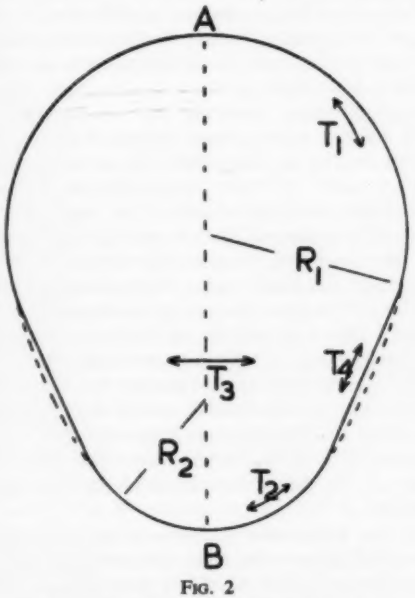

Fig. 2

An idealized section of a full-time uterus.

It is now necessary to outline one physical principle. Fig. 3 shows a fluid which is bounded

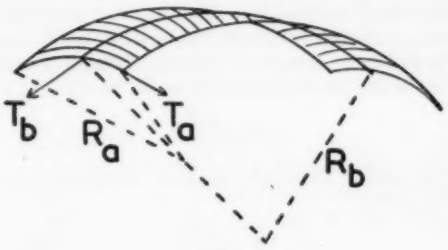

Fig. 3

A surface curved in two directions.

by a stressed membrane that is curved in two dimensions. It has a radius R_a in one plane set at right angles to the surface of the membrane and a radius R_b in a second plane at right angles to the first and also at right angles to the membrane. The internal stress in the membrane is T_a along the line in which the first plane meets the membrane and T_b along the line in which the second plane meets the membrane. This internal stress is defined by saying that if a line one centimetre long is drawn in the membrane at right angles to the direction of T_a then the two halves of the membrane on either side of the line are exerting a force of T grammes upon one another. It can be shown from first principles that the fluid in contact with the membrane described above is under a pressure of "p" g. per square centimetre where

$$p=\frac{T_a}{R_a}+\frac{T_b}{R_b}$$

In the specific case of a spherical membrane such as a soap bubble $T_a=T_b$ and $R_a=R_b$ whence

$$p=\frac{T_a}{R_a}+\frac{T_a}{R_a}=\frac{2T_a}{R_a} \text{ or } T_a=\frac{p.R_a}{2} \quad (1)$$

In the specific case of a cylindrical portion of a balloon, R_a is the radius of the cylinder and R_b is infinite because the cylinder is curved in only one direction.

$$\text{Thus} \quad p=\frac{T_a}{R_a} \text{ or } T_a=p.R_a \quad (2)$$

The tension T_b cannot be determined without further information being given though usually it is equal to $pR_a/2$ because it is holding the two curved ends of the balloon together.

When these relationships are applied to the simplified uterus of Fig. 2 we find that there are four stresses in different parts of its walls. As the fundus is spherical equation (1) applies and the fundus has a uniform stress T_1 where

$$T_1=\frac{p.R_1}{2} \quad (3)$$

Throughout the lower segment conditions are similar and

$$T_2=\frac{p.R_2}{2} \quad (4)$$

The conical mid-section has a curvature which varies from R_1 to R_2 in the one direction and which is infinite in the other direction. Thus in the one direction equation (2) applies and T_3 varies from

$$T_3=p.R_1 \text{ to } T_3=p.R_2 \quad (5)$$

In the other direction $T_4=T_1$ where it balances the pull of the fundal dome and $T_4=T_2$ where it balances the pull of the lower segment dome.

The proportions of the average uterus are such that $R_1=3R_2/2$. If we therefore substitute for R_2 in equation (4) and then eliminate R_1 by means of equation (3) we obtain

$$T_2=\frac{2T_1}{3} \quad (6)$$

$$T_3=2T_1 \text{ (at max.) and } \frac{4T_1}{3} \text{ (at min.)} \quad (7)$$

$$T_4=T_1 \text{ at max. and } 2T_1/3 \text{ at min.} \quad (8)$$

This set of relations must hold when the uterus is not in active contraction (when the tonus of the muscles is maintaining the shape) and also when the uterus is actively contracting. If therefore by "activity" is meant the fractional increase in tension which is produced when the muscle changes from the state of "tone" to the state of active contraction, then everywhere the activity of the uterine muscle must be the same, for the change in stress at contraction must be proportional to the stress already existing due to the tone of the muscle, the factor of proportionality being everywhere the same. If, however, by "activity" is meant the actual stress produced in the tissue, then the calculations above show that the highest stresses are found in the mid-segment of the uterus and are stresses whose directions are round the cone. There is a gradient of stress down the cone but the actual values are higher than the stresses experienced in the fundus of the uterus.

Consider now what would happen if the fundal muscle were to contract while all the other muscle fibres did not (the most severe case of gradient of activity from fundus to cervix). In order to preserve equilibrium in the uterus the non-contracting tissues must stretch so that the parallel elastic components of each muscle may exert a true elastic force. This stretching takes place by the whole uterine wall bulging into a more spherical shape, as shown in Fig. 4. This makes T_4 act on a curve with a radius of finite value whereas, before, this radius had an infinite value, and so the internal pressure will rise. A second process will be that the fundal muscle will shorten in order to stretch the elastic tissue of the lower portion of the uterus. It is, however, physiologically well known that a shortened muscle is not capable of exerting as great a force as a muscle where the length is maintained during activity. Thus the contraction of the fundal muscle would cause the value of the maximum force available to be diminished and this would reduce the effectiveness of the dilatation produced by the contraction.

It has never been maintained by any writer that the fundus is the only portion of the uterus that contracts, but what has been shown here in an extreme form still applies in a lesser degree

FIG. 4

A uterus in which the fundus has contracted but the rest of the uterine wall has not. The dotted line shows diagrammatically the change in shape which would take place.

to the theoretical case of a gradient of activity. A uterus which experienced a gradient of activity from the fundus to the cervix would (*a*) show considerable distortion in shape at every contraction, the lower segment becoming enlarged, and (*b*) produce lower values of internal pressure during each contraction than would be the case if all parts of the uterine wall contracted actively.

The next step is to examine the effect of inactivity of the lower segment upon the dilatation of the cervix. The cervix, at the commencement of labour, is still tube-like so that the pull of the lower segment upon the uppermost part of the cervix dilates this portion and this uppermost portion, in stretching, passes on a smaller dilating force to the next element of the cervix below it, so that the cervix dilates first at the top and then progressively downwards as is usually observed clinically. The mathematical treatment of this process is involved and will not be attempted here, but the simpler case of a cervix consisting of a compact elastic ring of radius "r" will serve to illustrate an important principle. If this compact ring, due to stretching, is under an internal stress of simple tension "t" grammes then it may be shown in a similar manner to the earlier calculations that

$$t=\frac{p.r.R.}{2} \text{ grammes}$$

where p is the pressure in the uterus, r is the radius of the ring and R is the radius of the lower portion of the uterus. Now it has been shown above that, due to the inaction of the lower segment, "p" is smaller than it would have been and "R" greater, so that it might be possible for the decrease in "p" to be balanced by the increase in "R". However, it can soon be shown that this is not so for the pressure can fall to zero if the lower segment walls are not elastic but "give" easily but the radius of curvature of the lower segment cannot increase to infinity. Therefore the rise in the value of "R" cannot balance the fall in the value of "p" and so the result of the inactivity of the muscles of the lower segment is to produce a smaller dilating force upon the cervix and to reduce the efficiency of the labour as stated above.

DISCUSSION

It is not proposed in this paper to give a long clinical discussion of evidence for or against the analysis given above, but one or two things should be said.

It should be remembered that clinical evidence is very often based upon operational or post-mortem observations of uteri which have been inefficient or have failed in their task so that the evidence is liable to be weighted in the direction of what happens when the lower segment muscles do *not* contract.

If it were possible, on the other hand, to observe the uterus of the normal case it might well be found that this thinning of the lower segment did not take place, as has been indicated above. It would be very valuable to gather clinical evidence which would point to a bulging of the lower segment of the uterus at each contraction. This is difficult information to obtain for the lower segment is so largely hidden in the depths of the pelvis that it is not so easily observed as the fundus which has always had the major attention. It should be stated also that anyone proposing to look for such a phenomenon should not look after the membranes

have ruptured. Rudolf and Ivy (1931) noticed that the bulging which attracted their attention disappeared as soon as the membranes ruptured and this is only to be expected for once the water has been expelled we are no longer dealing strictly with a hydrostatic phenomenon. There is no bulge because there is no water to fill the bulge.

There is a good deal of evidence of lower segment tissue being found to be much thinner than upper and mid-segment tissue at Caesarean section, and of finding the lower segment tissue paper thin and bulging. A good deal of this can be explained as due to ineffective uteri but it must also be remembered that the analysis attempted in the previous section was a very simplified one, the idealized uterus being given the shape of a peg top, with the result that at the junction of fundal dome with mid-segment cone there is a sudden jump in the stress in the direction round the uterus at right angles to the axis. In the actual uterus it is very likely that the maximum stress round the uterus is not near the fundus but at the point of longest radius of curvature, on the dotted line near T_4 in Fig. 1 and that the stresses gradually increase from the fundus down to this point of maximum curvature. This increase in stress could be sustained by giving the uterine wall an increasing thickness from the fundus down to this point and then reducing the thickness again towards the lower segment where the radius of curvature decreases again, with the result that equal muscle activity throughout the uterus would produce the stresses shown in equations 6, 7 and 8. The difference in thickness between lower and mid-segment has often been commented upon because it is frequently observed in Caesarean section. The change in thickness at the meeting place of fundus and mid-segment is not so often observed.

The description given above has not attempted to deal with the modification of the uterine wall as dilatation of the cervix proceeds, but a general consideration will show that the muscle fibres of all three segments should progressively shorten, in this way allowing the stretched fibres of the cervix to pass round the curve of the foetal head until the lowest rim of the cervix has dilated sufficiently for the foetal head to pass through. In this process the fibres of the lower segment slowly change from those which originally composed the lower segment to those which originally composed the cervix, so that inspection of the lower regions of the uterus at almost full dilatation should reveal a very thin lower segment with a much thickened mid- and fundal segment. This is the condition described clinically in the obstetrical textbooks.

There is of course much more to be considered in the analysis, such as the cause of inefficient action, the mechanism of the contraction ring, and other abnormalities. It would, however, be unwise to proceed further until a theory of efficient and normal action is properly based. What seems to be necessary is a study of the relative thickness and elastic properties of different parts of the uterine wall at term and the development of a method of observing the relative movements of different parts of the uterine wall during the contractions of labour. Work is proceeding in these directions, which it is hoped will strengthen the views here presented or at least provide evidence of how they should be modified.

Acknowledgments

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ADENOMATOID TUMOUR OF THE FALLOPIAN TUBE*

BY

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INTRODUCTION

ADENOMATOID tumour was the name suggested by Golden and Ash (1945) for a rare and interesting benign tumour which is found in the genital tract in males and females. Commoner in the male, it affects the epididymis, spermatic cord and testicular tunics; in the female, the uterus and Fallopian tubes are affected.

In the Fallopian tube the tumour has no symptomatology, and it is invariably an accidental finding at operation or post-mortem. The average age of recorded cases is 35 to 45 years. It grows slowly in the muscle wall and never attains a size exceeding a few centimetres in diameter. It forms a rounded unencapsulated tumour of firm consistency, which cuts like a fibroid and is grey or whitish yellow in colour. The histological appearances are quite distinctive and it is now accepted by pathologists as a separate entity. Its main interest to the gynaecologist lies in the fact that it can be mistaken for malignancy, but this is only likely to occur if one is unaware that such a tumour exists.

CASE HISTORY

In this instance the tumour was found in a 42-year-old multipara, who attended the clinic in March, 1953 and complained of pain in the vulva, dyspareunia, menorrhagia, metrorrhagia and continuous backache. She had had a vaginal plastic operation 6 years previously. On examination the cervix contained a small avascular polyp, and the uterus was bulky and retroverted. A hard nodule was felt on the right side and this was thought to be a fibroid.

Curettage and removal of the polyp was done, and section of the tissues showed no evidence of malignancy.

Laparotomy was performed on 16th November, 1953, and bilateral salpingo-oöphorectomy and total hysterectomy was done. The nodule felt on bimanual examination proved to be a hard tumour in the distal part of the right Fallopian tube. The patient made an uninterrupted recovery and has remained well since.

PATHOLOGICAL FEATURES

Naked-eye appearances

The specimen consisted of the uterus and appendages. The cervix uteri showed scarring; the uterine body appeared normal. Both ovaries contained follicular cysts. The left tube was normal. The lateral part of the right tube, just proximal to the fimbriated opening, showed the presence of an oval tumour measuring approximately $2 \times 1\frac{1}{2} \times 1\frac{1}{4}$ centimetres (Fig. 1). The growth was of a uniform pale yellow colour and of moderately firm consistency; it was within the upper wall of the tube and displaced the tubal lumen to one side.

Microscopic appearances

Tubal tumour. This was found to be made up of large numbers of gland-like spaces running in all directions and separated from each other by

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a small amount of loose fibrous stroma (Fig. 2). Many of the spaces were lined by cubical or columnar epithelium and had a narrow lumen; these spaces sometimes appeared as solid cords or nests of cells if the plane of section did not cut the lumen. Other spaces were wide and dilated and had a much more flattened lining. None of the cells was ciliated (Fig. 3).

The nuclei of all the cells were similar, being round or oval and showing a fairly heavy chromatin network, without any aberrancy or mitotic activity. Some of the nuclei showed vacuolation.

The cytoplasm of the cells was acidophilic, and there was a strong tendency for cytoplasmic vacuolation to occur; in some instances vacuolation gave the affected cell a "signet-ring" appearance while, not infrequently, groups of cells were so vacuolated that they were separated from one another only by thin cytoplasmic strands (Fig. 4). Fusion of vacuoles of adjacent cells was also common and it seemed clear that many of the wide spaces were formed by this coalescence of vacuoles. This explained why the boundary cells of these wide spaces were flattened and, on examination, many of the free margins of those cells were, in fact, found to be ruptured and ragged. The vacuoles did not show the staining reactions of mucin, glycogen or lipid.

The spaces of the tumour frequently contained a small amount of granular acidophilic material or occasional desquamated cells. With mucicarmine, a little of the granular material was faintly mucin-positive.

Reticulum stains showed the presence of condensed reticulin fibres round the tumour spaces. With the periodic acid Schiff method, the appearances indicated that the spaces had a basement membrane on which the lining cells were set.

Frozen sections stained with Sudan IV showed the presence of a small amount of lipid in the stroma, mainly situated within phagocytes.

The tumour was not encapsulated and extended internally right to the base of the mucosal folds of the tube; it did not, however, invade the mucosa which was intact in all the sections examined. Externally the appearances varied: in some areas there was a fair thickness of the muscular coat between the tumour and the serous coat, while in other areas the tubules of the tumour extended between the muscle bundles to just beneath the serosal lining. No evidence of direct continuity with the peritoneal surface was seen.

A fairly heavy lymphocytic infiltration, partly follicular in arrangement, was present in the serous coat in relation to the growth.

Smooth muscle did not form part of the tumour, but it was noted that a few of the small arteries of the growth showed abnormally thick walls.

In all, the appearances were those of a benign tumour with an adenomatoid structure.

Ovaries

Sections showed follicular cysts.

Uterus

No abnormality was found.

Historical

The Fallopian tube is the part of the genital tract least affected by neoplastic disease. Primary malignant disease is rare and accounts for less than 0·5 per cent of all genital malignancy; the total of genuine recorded cases probably does not exceed 500. Benign tumours are even more rare, and a careful scrutiny of the British literature has failed to reveal a single case with features resembling the one we describe. The last recorded simple tumour was diagnosed as an adenomyolipoma by Wilfred Shaw (1928), and from the general description and photomicrographs it was clearly not adenomatoid.

In the foreign literature a small number of benign tumours have been reported, and they have been variously described as lymphangioma, mesothelioma, adenomyoma, lymphangioendothelioma, lymphatic-reticuloendothelioma and sometimes carcinoma or adenoma; the majority have been diagnosed as lymphangioma.

In 1939, Sanes and Warner published a case of lymphangioma, the general features of which, together with a very detailed histological description, leave no doubt whatever that it was identical with the specimen we present. They reviewed the literature up to that time and

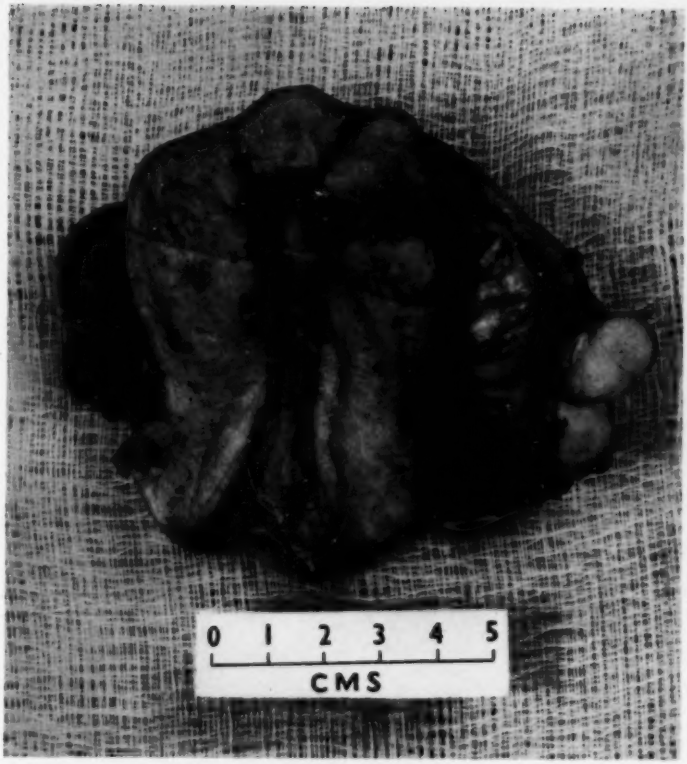

FIG. 1

Uterus and appendages showing adenomatoid tumour of distal part of right Fallopian tube.

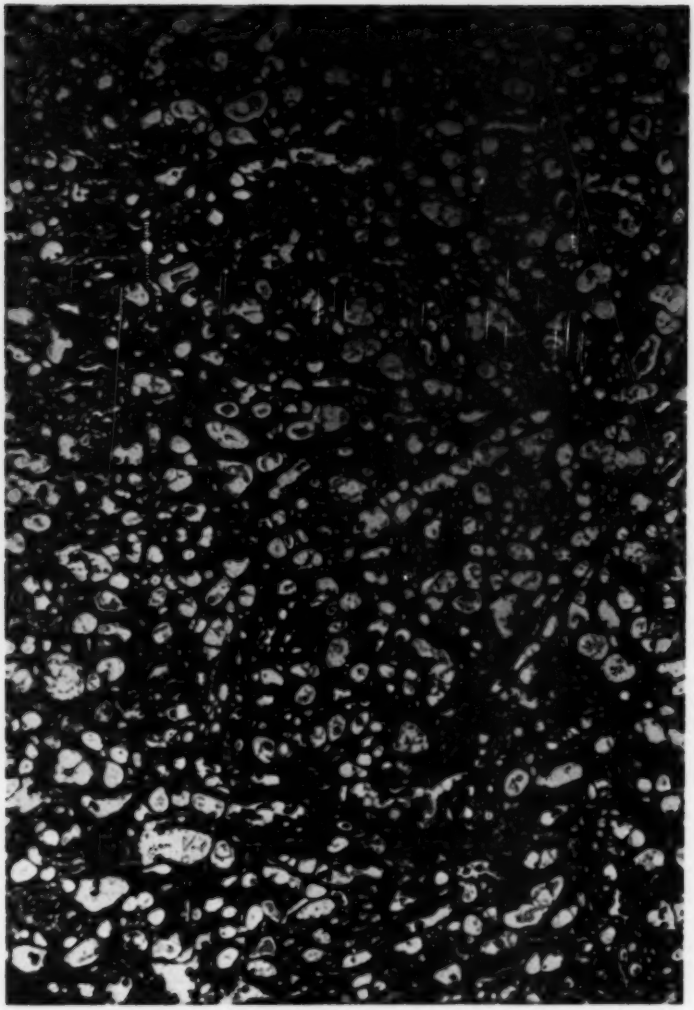

FIG. 2

General view of tumour showing characteristic pattern of numerous closely set small spaces; the superficial resemblance to lymphangioma is obvious. Haemalum and Eosin. ×130.

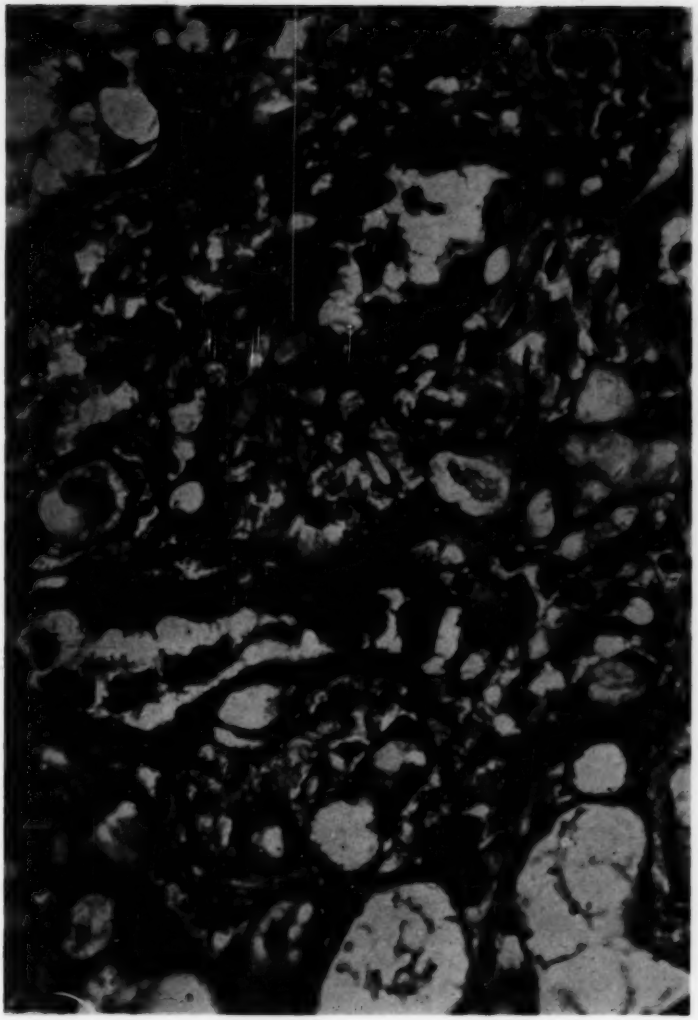

FIG. 3

Gland-like spaces lined by cuboidal cells together with dilated spaces lined by flattened cells. Cytoplasmic vacuolation of the cells is well seen. Haemalum and Eosin. ×900.

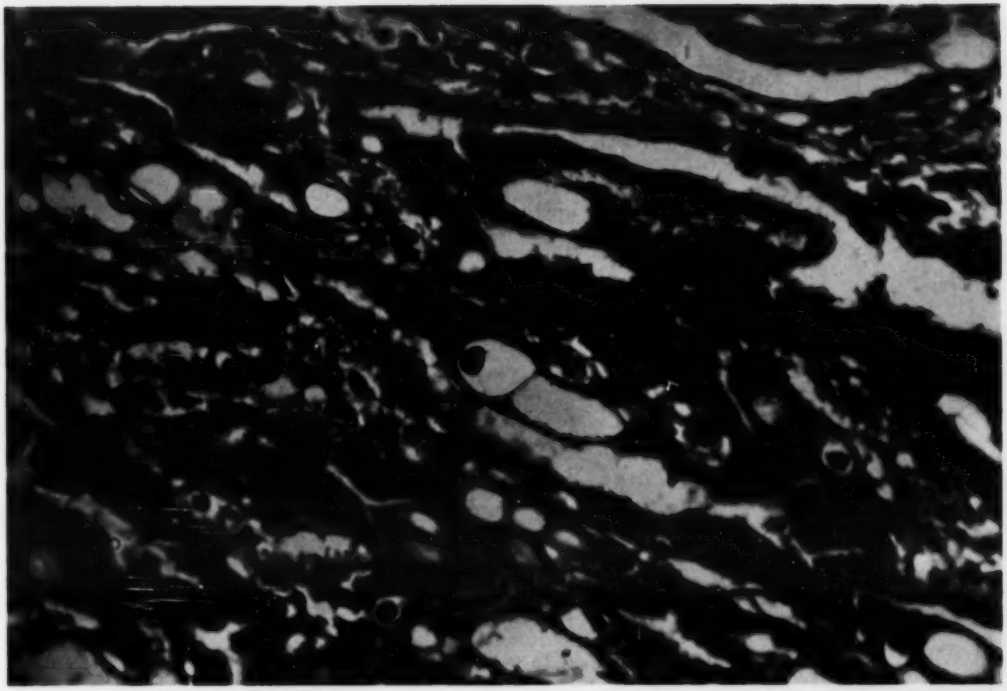

FIG. 4

Gland-like spaces cut more longitudinally. Vacuolation is very well seen in two cells lining a space in the centre of the field; only a thin cytoplasmic bridge separates the cells. Haemalum and Eosin. ×900.

found 17 cases of lymphangioma of the tube, only 3 of which were from the American continent, and they discussed at some length the presence of cuboidal and columnar cells in the tumour. They made it clear that they had difficulty in reconciling the presence of these cells in what they regarded as a tumour of endothelial origin and, what is more, went on to say that epithelial-like cells of the same type were found in the previously recorded cases of Hohne (1901), Dienst (1905), Kermauner (1907), Franz (1910), Dietrich (1918), Schiffman (1929), Nicod (1934), and Szathmary (1937). This disclosure puts it beyond doubt that many of the so-called lymphangiomas in the older literature were, in fact, adenomatoid tumours.

In 1943 Newton Evans reported 4 cases which he classified as mesothelioma. One of these tumours was in the Fallopian tube; one was under the peritoneal surface of the uterus; and two were from the epididymis of the testis of the male. He decided on a mesothelial origin, as he believed he was able to show direct continuity between the tumour cells in the uterus and the covering peritoneal coat.

Golden and Ash in 1945 described 15 cases of adenomatoid tumour, 2 in the Fallopian tube and 13 in the epididymis. They discussed the presence of cuboidal cells and insisted that they were epithelial and not mesothelial or endothelial. They stated that the characteristic feature of this tumour was epithelial tissue which tended to form gland-like structures and therefore the growth should be called an adenoma, but because of uncertainty concerning the pre-existing glandular structure from which it arose, they proposed the term adenomatoid. Connally (1946) described what he termed a mesonephroma of the Fallopian tube which histologically and in all other respects was typically adenomatoid. In this instance it was suggested that the tumour originated from mesonephric tubules and this genesis has been postulated by others. The views expressed by Golden and Ash were strongly supported by Ragins and Crane in 1948 when they reported 3 cases in the Fallopian tubes. Their cases were similar in all respects and all showed the characteristic histological pattern. They regarded the tumour as primarily an epithelial tissue and, as its origin was in doubt, they accepted and approved the name adenomatoid.

Lee *et al.*, of the Mayo Clinic, however, did not agree with this view, and in 1950 they published a series of cases which included 20 in the epididymis and adjacent tissues, and 2 in the Fallopian tube. They supported Evans and favoured a mesothelial origin. They also, like Evans, stated that this tumour is found in the uterus and established continuity between the cells lining the spaces and the overlying peritoneum. In all, they found 12 uterine tumours which had the same features as the tumour elsewhere. In one case they found a tumour of this type in the wall of an ovarian cyst, and they referred to similar cases which were reported by Siddall and Clinton (1937), Morehead (1946) and Ashworth (1948). Their review of the literature revealed that 64 cases affecting the male genital tract had been reported prior to their publication. Efskind (1952) reported a single case of a Fallopian tube tumour and adhered to the epithelial origin. He described the possible histogenesis at great length and was of the firm opinion that it arose from Müllerian vestiges. Willis (1953) confirmed the statement originally made by Masson *et al.* (1942) that these tumours of the epididymis and Fallopian tube were identical, and he classified them as adenomatoid tumours of Müllerian vestiges. His belief in a Müllerian origin was influenced by the findings of Sundarasivarao (1953) who was able, in one tumour, to show transition from papillary tissue identical with appendix testis (which is unquestionably Müllerian) to the usual tubular adenomatoid structure.

In addition to the authors mentioned, Leach (1950) has reported one case of Fallopian tube tumour which, together with the present case, brings the total to 13. This figure does not include any of the 17 cases of lymphangioma referred to by Sanes and Warner.

Comment

Excepting the recognition of a basement membrane in our specimen, there are no new features to shed light on the genesis of this group of tumours, and we do not propose to elaborate any of the opinions which have been fully discussed elsewhere. At the outset let it be

stated that we accept the view that fundamentally this tumour is an epithelial structure, and we regard the presence of a basement membrane and vacuolation in the cells as strong supporting evidence. An endothelial origin is no longer tenable, and the testimony so far evinced in favour of a mesothelial origin is also unconvincing. Proof is still wanting that mesothelium can produce epithelial-like neoplastic tissue, and the failure to demonstrate similar tumours in other serous cavities appears to be insurmountable. On the contrary, the sharp location of these tumours to the genital tract in both sexes, points strongly to a vestigial origin. In the Fallopian tube the tumour clearly originates in the muscle wall, and the absence of muscle in the centre of the growth indicates that it is an expansile tumour and not an invasion from the serosa or mucous membrane. Likewise there are no grounds for believing that these tumours arise from Wolffian relics, and the arguments advanced by Efskind against this possibility are entirely acceptable to us. Willis and Sundarasivarao, more recent contributors, have expressed strong convictions, supported by substantial evidence, of a Müllerian genesis, and we believe their observations approach as near to the truth as it is possible to go. Nevertheless, in the absence of absolute proof, there is every reason to retain the designation of adenomatoid tumour.

Summary and Conclusions

(1) A case of adenomatoid tumour of the Fallopian tube is described and, as far as can be ascertained, it is the first to be reported in the British Isles.

(2) This small tumour, which is found in the genital tracts of both sexes, has a precise histological pattern and is now accepted as a pathological entity.

(3) It is benign and by its gross and detailed pathology is easily distinguishable from malignant disease.

(4) The literature is reviewed and the aetiological possibilities outlined.

(5) The tumour is believed to arise from Müllerian vestiges.

We would like to thank Mr. W. H. Jones and Miss A. Dryden for technical and clerical assistance.

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SQUAMOUS CELL CARCINOMA OF MULTICENTRIC ORIGIN, INVOLVING CERVIX, UTERUS AND FALLOPIAN TUBES

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THE mode of origin of tumours is not only of interest to the pathologist, but is also of considerable practical surgical importance. Cohnheim (1889) and later Ribbert (1904) postulated that a tumour arises from a single cell or group of cells, and that all the cells of the tumour are direct descendants of the parent cell or cells. Mallory (1923), Kettle (1925) and other leading pathologists accepted this view of tumour origin, but it has never passed unchallenged, and Willis in a series of papers (1944, 1945, 1948) has shown it to be untenable. Willis considers that "tumours arise from small or large fields of tissue and enlarge not only by cellular proliferation, but also by progressive neoplastic conversion within these fields". This conversion may occur at a number of points within the field. Thus the potential area for neoplasia may be of far greater extent than the actual tumour, a fact which the surgeon must appreciate when radical treatment is undertaken.

This field theory of tumour origin is as applicable to the genital tract as to other parts of the body. In 1897 Hauser described a recurrent carcinoma of the vulva arising progressively over a wide area. Similarly the occasional occurrence of 2 tumours simultaneously may be an example of multifocal origin rather than mere coincidence.

The following case is not only unusual in itself, but is of importance in that it illustrates and supports Willis's concept when applied to a tumour of the female genital tract.

CLINICAL FEATURES

A woman aged 64 years was admitted to hospital with a 3 months' history of profuse yellow discharge from the vagina occasionally accompanied by bleeding, and dragging pains in the lower abdomen. The patient suffered from chronic bronchitis but otherwise her past medical and surgical history was not of note. She had had one child, and had reached the menopause at 49 years of age. On pelvic examination the cervix appeared healthy, but the uterus was bulky and there was a little bleeding through the cervical os. No other abnormality was found. On curetting the body of the uterus fragments of squamous cell carcinoma were obtained.

Panhysterectomy with bilateral salpingo-oöphorectomy was performed. The immediate post-operative course was satisfactory, but on the 5th day the patient suddenly became acutely dyspnoeic and died within a few minutes.

PATHOLOGICAL FINDINGS

At autopsy there was a massive pulmonary embolus. The operation site was healthy, and no secondary deposits of carcinoma were found. There were no other relevant abnormalities.

The surgical specimen received in the laboratory consisted of an opened uterus with both appendages. The surface of the cervical canal had lost its normal architecture and was irregular and rough. The appearances were those of a

carcinoma superficially invading the cervix. The endometrium, Fallopian tubes and ovaries showed no macroscopic abnormality.

On microscopy the greater part of the portio vaginalis of the cervix is covered by normal squamous epithelium. Near the external os, however, there is an abrupt change in the structure of the epithelium; the superficial third becomes parakeratotic, and the inner two thirds are composed of deeply basophilic cells. In this deeper layer the usual progression from stratum germinativum to surface layers can be distinguished, but it is indistinct and frequently interrupted by marked irregularities, the cells varying in size, shape and nuclear structure. Multinucleated cells are fairly numerous, but mitoses are infrequent. The basement membrane in this region appears intact, and the appearances are those of non-invasive carcinoma of the cervix. This change extends upwards through the external os for a distance varying from 1 to 1·5 cm. where a frankly invasive squamous cell carcinoma develops. This surrounds the cervical canal and extends into the body of the uterus. The tumour invades the wall of the canal for about half its thickness but extends through the whole depth of the anterior wall of the corpus uteri. In places the tumour shows a little evidence of keratinization. Neither endocervical nor endometrial glands can be found in the canal or lower part of the corpus uteri.

The fundus and cornua are lined by a stratified squamous epithelium which is thickened and closely resembles the area of non-invasive carcinoma described in the cervix, except that there is no parakeratosis. Isolated islands of invasive carcinoma are seen, however, in the immediately subjacent uterine muscle. Endometrial glands are very few. Occasionally they are surrounded by normal stroma, but more frequently they are partly incorporated in the thickened squamous epithelium (Fig. 1).

This thickened stratified epithelium extends up into the isthmic portion of the left tube and to the ampullary part of the right (Fig. 2). The appearances are very similar to those in the fundus uteri, except that no invasion can be detected, even after serial sectioning, and that more glands are incorporated in the thickened epithelium. The marked ichthyotic changes end fairly abruptly, but nearer the fimbriated end of the tube certain significant changes can be seen. In places the subepithelial zone of cells becomes thickened to form plaques which push aside the reticular framework of the adjacent connective tissue (Figs. 4 and 5), and in one area such a plaque shows variation in nuclear structure similar to that of the ichthyotic epithelium (Fig. 3).

Discussion

Plaques of cells with either a superficial or a close resemblance to squamous epithelium are sometimes seen in the senile endometrium or in association with atypical endometrial hyperplasia, and their occasional presence in adenocarcinoma of the corpus uteri has led to use of the term "adeno-acanthoma". When the normal endometrium is extensively replaced by an apparently true squamous epithelium the term ichthyosis uteri is used. Such a change is of comparatively rare occurrence, and was recently reviewed by Motyloff (1950). We have, however, been unable to find previously described either an example with such widespread metaplasia involving both tubes and uterus as our case shows, or one in which the metaplastic epithelium appeared for the most part carcinomatous.

The practical importance of the case lies in a consideration of two features: the site of origin of the tumour, and its mode of development.

1. *Site of origin.* If the tumour arose from a single primary focus then its wide extension must have been either through the superficial lymphatics of the uterus, or by an intra-epithelial migration of tumour cells. Lymphatic spread in this particular case appears unlikely, for in the lower part of the cervical canal and in the Fallopian tubes the process is entirely superficial. Intra-epithelial extension similar to that suggested in Paget's disease of the breast, or sub-epithelial spread between epithelium and basement membrane might occur. Microscopically, however, the appearances are of irregularities throughout the epithelium, rather than of cells of essentially normal structure and arrangement with occasional malignant cells scattered among them. Strong additional evidence against origin from a single focus is the presence of

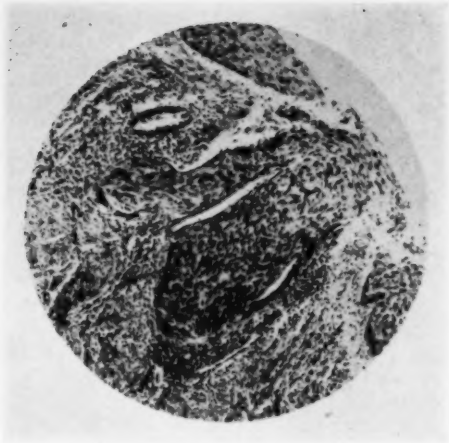

FIG. 1

The section is taken from the fundus uteri and shows an island of squamous epithelium incorporating two endometrial glands. Haematoxylin and eosin. ×60.

FIG. 2

A transverse section of the isthmus of the right Fallopian tube showing the thick lining of stratified squamous epithelium. Haematoxylin and eosin. ×11.

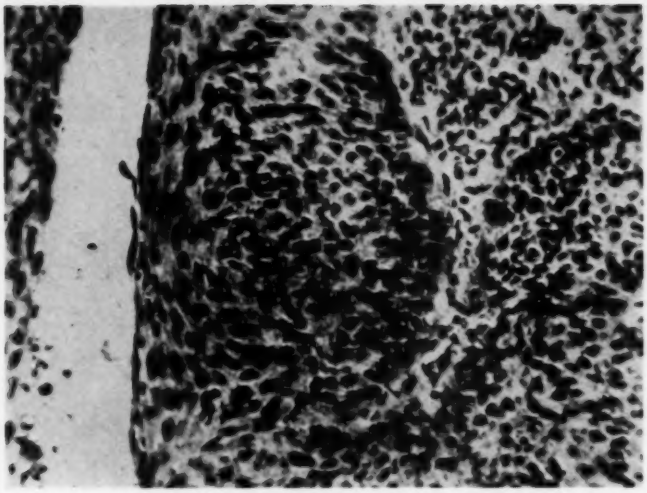

FIG. 3

An area of the epithelium lining the Fallopian tube. Note the progression of the cells from columnar at the base to flat at the surface. In the middle zone the arrangement is irregular and the nuclei show variation in size and chromatin content. Haematoxylin and eosin. ×430.

FIG. 4

A section of the tube, beyond the area of ichthyosis, showing a plaque formed of sub-epithelial cells pushing aside the reticular framework. The plaque is infiltrated by lymphocytes. Haematoxylin and eosin. ×225.

F.A.L., A.S.W.

FIG. 5

Another plaque similar to that of Fig. 4 in which there is much less infiltration by lymphocytes. The columnar epithelium overlying the plaque has been lost. Haematoxylin and eosin. ×225.

isolated areas of metaplastic epithelium in the tubes. No continuity between these islands and the main tumour can be established even after examination of serial sections. Thus the tumour appears probably of multicentric origin.

2. *Mode of development.* Motyloff (1950) described a case of ichthyosis uteri which was under observation for 5 years. Initially endometrial curettings showed "mild glandular hyperplasia" and contained small foci of stratified epithelium showing a state of differentiation not unlike that of carcinoma *in situ*. The patient was treated by the insertion of 100 mg. of radium for 18 hours. The uterus was removed 5 years later, and the entire endometrium was found to be composed of stratified squamous epithelium. Motyloff considered that the transformation of the endometrium from a glandular to a stratified squamous epithelium in this case was due to differentiation of ectopic foci of basal cells as described by Meyer (1910a and b, 1923).

Carmichael and Jeaffreson (1939) drew attention to the small rounded basal cells which frequently surround endocervical glands and regarded them as a reserve depot from which regeneration of cervical epithelium might occur. Howard, Erickson and Stoddard (1951) consider that intra-epidermal carcinoma of the cervix may arise from these basal or "reserve" cells. Our Fig. 4 corresponds closely to Figs. 4 and 5 of Howard *et al.*, who describe them as showing hyperplasia of reserve cells in the endocervix. Unfortunately it is uncertain whether such basal or reserve cells exist beneath the epithelium of the Fallopian tube. Standard textbooks of histology such as those by Maximow and Bloom (1952), and Von Möllendorff (1927) make no reference to such cells. We have examined a small series of tubes from both adults and neonates, but have been unable to establish definite evidence of the existence of such groups of cells, although the normal tendency to pseudo-stratification of the tubal epithelium makes assessment difficult.

Kaufmann (1906) does not accept Meyer's concept of epidermidization of the cervix by proliferation of heterotopic foci, but considers that the stratified epithelium originates from the columnar epithelium of the surface, which grows downwards and is subsequently converted to stratified squamous epithelium. If the tubal epithelium does not contain reserve or basal cells then the plaques described in the tube in the present case may arise by a mechanism such as that suggested by Kaufmann.

Summary

The practical implication of multicentric tumour origin is stressed.

A case of squamous cell carcinoma involving cervix, uterus and Fallopian tubes is described.

The site of origin of the tumour is discussed and it is shown to be probably multicentric.

The importance of basal or "reserve" cells in the development of the carcinoma is considered.

We should like to thank Dr. J. W. A. Hunter for permission to record the clinical findings and Professor W. I. C. Morris for his advice and criticism.

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A NOTE ON MENSTRUATION AND CONCEPTION DURING LACTATION

BY

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THE proportion of women in whom menstruation reappears before the end of lactation is variously recorded in the literature as 41 per cent (Booth, 1935; Robinson, 1943), 65 per cent and 75 per cent in white and coloured populations respectively (Peckham, 1934), 57 per cent and 73 per cent in primiparae and multiparae respectively (Sharman, 1951). Grünberger (1948) went so far as to doubt whether the cycle is retarded in lactating women. These observations are somewhat surprising when we recall that in most experimental animals ovarian activity is effectively suppressed during lactation, for example in the macaque (Hartman, 1932) and baboon (Gillman and Gilbert, 1946).

Two reasons may be suggested for the high incidence of menstruation during lactation in reported clinical data: (*a*) Inhibition of the cycle cannot be prolonged indefinitely, for, if the stimulus of suckling is maintained in lactating rats by fresh litters, the cycle eventually reappears (Selye and McKeown, 1934). It would therefore be expected that the frequency of menstruation before weaning would be related to the duration of lactation; that this is the case is confirmed by Peckham's data. The high incidence of menstruation during lactation in some reported series is partly accounted for by a high mean duration of lactation, for example more than half the women whose histories were examined by Peckham (1934) fed their children for more than 7 months, and all of the 413 women upon whom Robinson's estimate (1943) is based fed their children for at least 8 months. (*b*) Also significant in relation to reports that the cycle frequently returns during lactation is the fact that as a rule no clear distinction has been made between the intervals for which children were wholly or partially breast fed. That it is the stimulus of suckling that inhibits the cycle is strongly suggested by the observations that suckling inhibits oestrus in non-pregnant rats (Selye and McKeown, 1934) and in lactating rats after all the main galactophores have been cut (Selye, Collip and Thomson, 1934). Hence, when the suckling stimulus is reduced—as it is when children are partially weaned—it is inevitable that inhibition of the cycle should be less effective.

The observations which follow are based on 1,227 post-partum women, for whom a history of menstruation and lactation was recorded. The sources of these data have been described previously (McKeown, Gibson and Dougray, 1953). Table I gives the number of bleedings which occurred during lactation (here interpreted as the period of breast feeding without artificial supplements). The history of menstruation or lactation was incomplete in 197 of the 1,140 women who did not conceive within a year of delivery. Of the remaining 943 women, 208 (22 per cent) had at least one period while their infants were fully breast fed. The proportion in whom the cycle returned during lactation increases as the duration of feeding increases, being 10 per cent for women who fed their children less than 3 months, and 48 per cent for women who fed their children more than 6 months.

The relatively low proportion of women in whom menstruation returned during lactation (22 per cent) is evidently accounted for in part by the short mean duration of lactation (only 26 per cent of mothers fed their children for more than

TABLE I

*Menstruation During Lactation**

Duration of Breast Feeding (days)	Number of Bleedings during Lactation								Percentage of Women who Menstruated during Lactation
	0	1	2	3	4	5	6 or more	Total	
0–	374	4	—	—	—	—	—	378	1
30–	141	16	—	—	—	—	—	157	10
60–	60	29	4	—	—	—	—	93	35
90–	32	16	18	—	—	1	—	67	52
120–	60	22	23	10	4	—	—	119	50
150	43	12	9	6	4	5	2	81	47
180+	25	7	4	3	5	3	1	48	48
Total	735	106	58	19	13	9	3	943	22

* Based on 1,140 women who did not conceive within a year of delivery.

4 months). It is also affected by the interpretation of lactation as the period of breast feeding without artificial supplements. Figure 1 shows the proportion of women in whom the cycle had returned at monthly intervals according to the method of feeding at each interval. For example, of mothers who at 4 months after birth were breast feeding, breast and artificially feeding or artificially feeding their children, the percentages who had menstruated (within the first 4 months) were 39·8, 56·8 and 95·3 respectively.

These observations suggest that in women, as in most experimental animals, menstruation is fairly effectively suppressed during the early months of lactation. It reappears in an increasing proportion of women as lactation proceeds, and returns more rapidly, even in the early months, if the child is partially weaned.

Since the end of lactation and reappearance of the cycle frequently coincide, it has been suggested that menstruation inhibits lactation. Engel (1947) noted that the milk supply has usually begun to decline before the onset of bleeding; but since ovarian activity precedes bleeding this in itself can hardly be accepted as proof that the cycle has no effect on lactation. More suggestive are the observations that in a small proportion of women regular cycles (usually anovular) continue throughout lactation, and in the rat the return of the oestrous cycle does not interrupt lactation if the stimulus of suckling is prolonged.

It seems clear that it is the stimulus of suckling which inhibits the cycle, and, since the effect can be demonstrated in the non-pregnant rat, it appears to be independent of lactation. It is probable therefore that the reappearance of menstruation in the early months of lactation is usually due to a reduction in the stimulus of suckling, which may be voluntary, or may result from use of artificial foods to supplement an

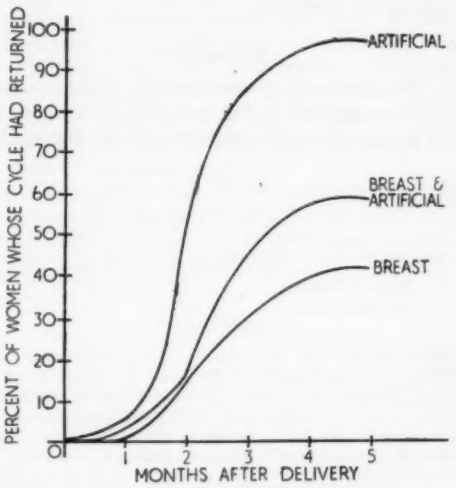

FIG. 1

Return of Menstruation related to the Method of Feeding.

inadequate milk-flow. If this explanation is correct ovarian activity does not interfere with lactation, and failure of lactation leads to a return of the cycle only indirectly because it results in a reduction of the stimulus of suckling.

Conception during Lactation

Although fertility is undoubtedly reduced during lactation, it is now evident that suckling is by no means as effective in preventing conception as it was once thought to be. Peckham (1934) noted that about 30 per cent of a group of post-partum women became pregnant during the 12 months after delivery; approximately two-fifths of them were still lactating at the time of conception (one-tenth conceived without having menstruated). Although based upon fertile women in poor economic circumstances, these rates indicate that, unless otherwise prevented, conception during lactation is not uncommon.

In our own series 87 (7 per cent) of 1,227 mothers conceived during the year after delivery; Table II gives their distribution according to (*a*) type of feeding at the time of conception, and (*b*) the number of bleedings preceding conception. Eight women conceived while breast feeding their children and 4 before the return of menstrual bleeding.

Summary

The frequency of menstruation during lactation is examined in 943 post-partum women. It is shown that menstruation is fairly effectively suppressed during the early months of lactation; it reappears in an increasing proportion of women as lactation proceeds, and returns more rapidly, even in the early months, if the child is partially weaned. Evidence is referred to which suggests that (*a*) ovarian activity does not usually interfere with lactation, and (*b*) failure of lactation leads to a return of the cycle only indirectly because it results in a reduction of the stimulus of suckling.

Eighty-seven of 1,227 post-partum women became pregnant within a year of delivery. Of these 87 women, 10 conceived while their children were being wholly or partially breast-fed. Of the 10 women, who became pregnant during lactation, 4 conceived before menstruation was re-established, 2 after a single bleeding and 4 after 2 or more complete cycles.

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Table II

*Conception During Lactation**

Type of Feeding at Conception	Number of Bleedings Preceding Conception												Total
	0	1	2	3	4	5	6	7	8	9	10	11	
Breast only	—	2	—	—	—	—	—	—	—	—	—	—	2
Breast and Artificial ..	2	—	—	1	2	—	1	—	—	—	—	—	6
Artificial only	2	—	10	14	10	7	12	6	7	5	5	1	79
Total	4	2	10	15	12	7	13	6	7	5	5	1	87

* Based on 87 women who conceived within a year of delivery.

A CASE OF SYMPODIA

BY

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MINOR abnormalities of the newborn baby are not infrequent, and are usually of such a character that by means of plastic surgery nature's mistakes can be eliminated to a large extent. These cases are therefore frequently reported, mainly because the technique of the surgery used is considered worthy of publication. Major abnormalities, on the other hand, which are incompatible with life, are all too frequently discarded as monsters, and being of no value clinically are not reported. When this case of sympodia, or mermaid foetus, was delivered, the literature was searched for a record of similar cases, but only one reference could be found, which included a pen sketch. It was therefore felt that this unusual type of abnormality was worthy of being placed on record.

The gestation had been normal, except for a threat to abort at the 8th week and a small amount of ante-partum haemorrhage at the 30th week, which was thought to be due to a large cervical erosion. At the 36th week the foetus was found to be presenting by the breech. Unsuccessful efforts to perform an external version were followed by labour a few hours later. The foetal heart was heard a few minutes before delivery, but when born the foetus showed no signs of life. The weight was 3 pounds 4½ ounces.

ANATOMICAL FINDINGS

At autopsy many gross congenital abnormalities were found. The left upper limb showed absence of radius and thumb; the right was normal. The two lower limbs had not separated, and appeared as one limb with a double structure in most parts (Figs. 1 and 2); the femora were present, apparently normal, but the fibulae were incomplete. The right tibia had only incompletely rotated, the left had not rotated at all. The small bones of the foot appeared deficient in numbers. In the pelvic bones, the ischio-pubic remus was absent on both sides, and the symphysis pubis was composed of a flattened bone. A rudimentary penis with scrotum was present at the back of the fused thighs. Both testes were found later inside the abdomen.

No trace of an anal opening could be seen and, on investigating the bowel from the abdominal cavity, it was found that the colon finished high in the left iliac fossa as a blind end; the remainder of the gastro-intestinal tract appeared distended, but structurally normal. Neither kidneys, ureters, urinary bladder nor urethra could be found. The pancreas, adrenals, liver and gall bladder appeared normal. Although the right lung was normal in outline and size, but not expanded, the left lung was absent; in its place was a small knob of tissue or lung bud on the end of a normal main bronchus. The larynx, trachea and pharynx appeared normal.

It is regretted that a fuller examination of the anatomical abnormalities was not made and recorded, but it was not at the time appreciated how rare this specimen was.

CASE HISTORY

The association of spontaneous abortion and foetal abnormalities is an accepted clinical entity, and some authors also postulate a relationship between sterility and the abnormal foetus. The mother's obstetric history tends to support the above statement. She was 37 years old, para 0+1, married 13 years. The husband's age was stated to be the same as her own. She booked at the antenatal clinic at the 25th week of the gestation, which had been normal so far, except for the threat to abort

previously mentioned. She had always been anxious to have a family, and contraception had never been practised. The only previous conception ended in 1947 in a spontaneous abortion at the twelfth week. In her past medical history, she had only suffered from childhood complaints.

On clinical examination, nothing abnormal was found. The mother appeared healthy and well developed. The blood pressure was 118/74 mm.Hg, the blood Rhesus positive and the Wassermann reaction negative. The uterine enlargement at each antenatal examination corresponded to the period of amenorrhoea, and at no time was there any reason to suspect abnormality of the foetus.

The puerperium was normal in every way.

Unfortunately all efforts to secure a seminal test of the husband for the purpose of assessing the percentage of abnormal forms were in vain.

FIG. 2
Right lateral aspect.

FIG. 1
The mermaid foetus. Anterior aspect.

CASE OF A VESICO-URETHRO-VAGINAL FISTULA

BY

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OBSTETRICAL vesico-vaginal fistula with destruction of the urethra and internal sphincter is found very rarely in this country owing to the generally high standard of the obstetrical service.

In the majority of cases the cure of these fistulae presents a most difficult problem in urological gynaecology. In dealing with this condition surgeons have usually found it necessary to advise and perform a transplantation of the ureters. The high mortality (over 20 per cent) and the shortened expectation of life are two of the many disadvantages of this operation and it should therefore be performed only as a last resort when all other methods have proved unavailing.

The desperate state of the patients suffering from incontinence and the difficulty of finding a means which will cure the patient without at the same time endangering her life is I feel sufficient justification for publishing this case. The combination of surgical procedures, as described below, has not been described in the literature as far as I am able to establish.

CASE HISTORY

Mrs. A.E., No. 56308, aged 45, was admitted on the 23rd September, 1952, to the Gynaecological Department of Bethnal Green Hospital.

Her history revealed that she had been admitted to a hospital in 1937 for her first confinement. After prolonged labour, lasting for 73 hours, she was delivered of a still-born full-time child by high forceps, resulting in a vesico-vaginal fistula with destruction of the urethra and the sphincters. A Caesarean section was apparently not performed in view of the presence of puerperal sepsis. The patient was transferred to another hospital where 2 unsuccessful operations were carried out in an attempt to close the fistula. A nervous breakdown ensued and she spent more than a year in a mental hospital, and when finally discharged refused any further treatment. She was completely incontinent and unable to go out to work.

The patient was a rather obese woman of poor mental capacity. A few days before the operation she was put on sulphasuxidine which was replaced by Terramycin. She was operated on on the 15th October, 1952, under spinal and general anaesthesia. The operation consisted of three main parts:

1. *Reconstruction of the urethra*, as described by C. H. Richardson, Houston Everett and te Linde was the first step. The edges of the fistula were excised. A "U"-shaped incision was made through the vaginal epithelium, the flap was freed and its edges approximated and stitched over a Frankis Evans plastic "oesophageal tube". (This tube is thin and has a smooth round end, whereas the usual type of Polythene tube has a sharp end liable to injure the mucous membrane of the bladder.) This new urethra was lifted and stitched into the fistula with interrupted catgut sutures. This solved the first problem of closing the fistula.

2. The second step consisted in *dissecting both gracilis muscles*. A long incision of the skin was made over the gracilis muscle on the inner aspect of the thighs from the knee up to the pubic bone, the insertion of the muscle, and into the vagina on the right side. On the left side the incision was stopped short of the pubic bone and the distal muscle end was pulled through a tunnel. The first technique seems to be more satisfactory. The distal ends were severed, brought under the urethra without interfering with their blood supply and stitched criss-cross to the pubic fascia. The gracilis muscles sling provides the tissue surrounding the fistula with a layer of well-nourished muscle tissue.

3. The third step consisted in an *interposition operation and a bilateral vaginal salpingectomy*. The vesico-cervical space was opened and the fundus of the uterus was brought down anteriorly. This revealed a bilateral chronic pyosalpinx, obviously the residuum of her puerperal sepsis 15 years before. A right salpingo-oöphorectomy and a left salpingectomy were performed and the fundus uteri was stitched to the periosteum of the pubic bones. The vaginal epithelium was closed with some difficulty. A double continuous drainage of the bladder was established, a urethral via the Frankis Evans tube and a suprapubic one via a self-retaining catheter. A transfusion of 2 pints of blood was given during the operation.

The patient made an uneventful recovery and was

discharged on the 27th November, 1952, to a convalescent home and was advised not to restart work or her married life for at least 3 months. But a day or two after admission to the convalescent home she discharged herself against medical advice, returned home, resumed her married life and went out to work, which in her case consisted in scrubbing floors. So far this does not seem to have had any adverse effect on the result of the operation and she is still continent.

Discussion

The gracilis pedicled flap is useful in helping to close the fistula by padding the newly-constructed urethra with healthy tissue, well supplied with blood. This operation alone might succeed in some difficult cases. This happened with one of our patients after 3 attempts with other methods had failed.

The interposition operation was added, therefore, in order to make sure that no stress incontinence remained or developed.

The question might be raised: why not rely on the interposition operation alone? If the hole in the bladder is patched up with the uterus it would be impossible to remove the uterus, should that become necessary for any reason at a later stage, without thereby producing another fistula. By inserting a layer of muscle between the bladder and uterus we have made the former independent of the latter.

Summary

(1) A case of an obstetrical vesico-vaginal fistula with destruction of urethra and sphincters is described.

(2) Two attempts to close the fistula—15 years earlier—failed.

(3) The case was cured by reconstruction of the urethra with the help of Frankis Evans plastic tube, a bilateral pedicled gracilis muscle flap and by a Watkins-Wertheim interposition operation.

(4) It is suggested that this combination of operative procedures might be useful in some of the "inoperable cases".

THIOURACIL GOITRE IN A NEWBORN

BY

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THE purpose of this communication is to record yet another instance of thyroid enlargement in the foetus due to thiouracil administration to the mother. This goitrogenic action of thiouracil and allied drugs has perhaps not received as much attention as it deserves, although since 1945 one or two cases were added almost every year to those already published.

LITERATURE

Keynes (1952), in a review of the subject, emphasized that where the drugs were given for a short time only during pregnancy the infants subsequently born proved to be healthy. But in 5 of his 6 cases the drug was given for longer periods and the infants were either cretinous or displayed congenital goitres. Although it would not appear that damage to the foetal thyroid gland is an inevitable result of thiouracil medication of the mother, yet the animal experiments of Freiesleben and Kjerulf-Jensen (1947) support the thesis that this sequel is likely to occur in a large percentage of cases. Eaton (1945) describes 2 pregnant women who were treated for thyrotoxicosis. In 1 the drug was stopped 4 weeks before the expected date of delivery and the infant was healthy at birth. In the other 200 mg. thiouracil was given throughout the pregnancy; the infant was born with an enlarged thyroid. The swelling subsided in the course of 3 months. Davis and Forbes (1945) recorded a hyperplastic thyroid in a foetus of 6 months, the organ being about twice the normal size and hyperplastic histologically. The mother died suddenly after having been on 200 mg. thiouracil on alternate days throughout her pregnancy. The patient of Frisk and Josefsson (1947) was treated with methylthiouracil during pregnancy, the dose being 300 mg. for the last 3 months. The only abnormalities of the infant at birth were retarded centres of ossification, but it became thyrotoxic in the second month with marked exophthalmos, which persisted for 5 months. This unusual development was due to increased secretion, after birth, of thyrotropic hormone by the infant's pituitary in order to stimulate the thyroid gland, the activity of which had been repressed during intrauterine life by the drug; the maternal thyroid hormone had apparently been sufficient for the infant's needs during that time and prevented pituitary overactivity before birth. Herrera (1948) recorded a goitre of at least twice the normal size in a stillborn infant, the mother having been on an unspecified dose of propylthiouracil from the fifth to the seventh months of her pregnancy. In 2 of Verel's (1949) cases the drug was stopped 2 and 4 months respectively before delivery and the children were normal at birth. In his third case thiouracil medication continued during pregnancy and the child was born with an easily palpable goitre which disappeared after 1 month. When re-examined at the age of 2½ years it had developed in a normal manner. A congenital goitre was likewise observed by Lund (1950), the mother having been on a maintenance dose of 1 g. of methylthiouracil every third day throughout her pregnancy. The thyroid swelling was still present at the age of 3 months, though otherwise the infant was normal. Elphinstone (1953) described in detail one of the cases (case 5) reviewed by Keynes. The mother had been on a daily dose of 200 mg. of methylthiouracil during pregnancy and puerperium. The infant displayed symptoms of severe hypothyroidism and in its subsequent development proved to be backward both physically and mentally. A quite similar case was recorded by Morris (1953), except that the infant had a palpable thyroid gland. Thyroid was given with marked clinical improvement and the child

appeared normal when discharged at the age of 8 weeks. The thyroid swelling had by then subsided. However, at the age of 8 months it developed signs and symptoms of a hydrocephalus, which the author presumed to be, in all likelihood, merely coincidental.

Case Report

The mother was 31 years of age, and had had a subtotal thyroidectomy for exophthalmic goitre in 1941. Since 1950 she had again shown mild thyrotoxic symptoms and had been since that time on a maintenance dose of 100 mg. methylthiouracil on alternate days. After a normal pregnancy she was delivered by forceps for transverse arrest on 2nd September, 1953, of a stillborn female infant weighing 3,660 g. (8 pounds).

At *autopsy* a bilateral swelling of the neck was clearly visible, and on dissection the enlarged thyroid lobes measured 3½ × 3 × 2½ and 3 × 2½ × 2 cm. respectively (Fig. 1). No congenital abnormalities were present in the thorax. The liver weighed 265 g., the spleen 42 g., the kidneys 16 and 18 g. and the adrenals 3½ g. each. The intestinal canal and especially the large intestines were dilated and filled with rather pale meconium. The peritoneum was hyperaemic throughout and there were many short adhesions between the bowel loops, and between the intestines and the abdominal wall. These consisted of serosa only and had not produced intestinal narrowing and obstruction. Death was due to intracranial haemorrhage owing to large bilateral tentorial tears.

Histological examination. All organs, except the thyroid, were normal. This showed a normal structure and marked venous congestion. No colloid was present and the lining epithelial cells had desquamated into the acinar lumina, but both these features are considered normal at birth. The nuclei, however, displayed considerable variation in size, were frequently hyperchromatic and a few mitotic figures were discernible (Fig. 2). A diagnosis of simple hyperplasia was made.

Discussion

This case again stresses the danger of thyroid damage in the infant when the expectant mother is treated during pregnancy with drugs of the thiouracil group, even if the dose, as in this case, is considered to be minimal. Reviewing the literature it becomes clear that, wherever possible, medication should be stopped early in pregnancy and Keynes's advice to resort to surgery in order to control the mother's thyrotoxicosis appears to be very sound. The thyrotoxic pregnant woman who has already undergone a previous subtotal thyroidectomy and is not responding to iodine will always constitute a difficult clinical problem. But, apart from these rather rare cases, it would seem wise to discontinue thiouracil treatment during pregnancy, although in many cases the infants' thyroid recovers and resumes its normal function in due course. However, it is interesting, in this connexion, to note that cases of permanent foetal damage, though only becoming manifest later, have been observed and the possibility of a causal connexion, though at present but speculative, cannot be entirely ruled out. In Elphinstone's (1953) case the infant proved to be backward, while Morris's (1953) case developed subsequently a hydrocephalus. This author considered that the development of the hydrocephalus was merely coincidental. But, in view of the finding of widespread serosal peritoneal adhesions in the above case, one wonders whether similar endothelial adhesions within the skull might not have been the cause of the hydrocephalus.

Summary

A case of thiouracil goitre in a stillbirth is described. An interesting additional finding were widespread serosal peritoneal adhesions. The mother had been on the small maintenance dose of 100 m. methylthiouracil 3 times weekly.

The literature is reviewed and the danger to the foetus of thiouracil treatment of the mother's thyrotoxicosis is again stressed, both as regards the immediate effects as well as possible delayed sequelae.

I should like to thank my colleagues Dr. L. W. Hale and Mr. P. N. Simons for the clinical details, and Prof. T. F. Hewer and Dr. O. C. Lloyd for arranging the photography.

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FIG. 1

Autopsy specimen, showing clearly the enlarged thyroid lobes.

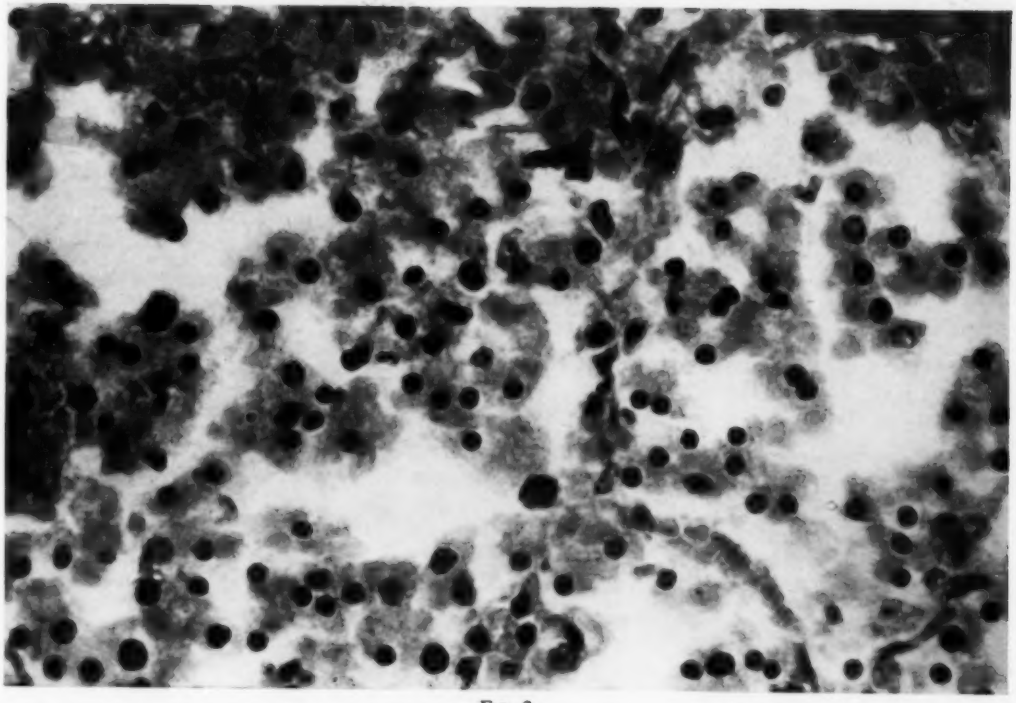

FIG. 2
High power view of thyroid parenchyma, displaying marked nuclear variation. ×1120.

METHAEMOGLOBINAEMIA IN THE NEWBORN

Probably Due to Phenytoin Excreted in Human Milk

BY

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AND

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IT is well known that certain drugs taken by a nursing mother may be excreted in the breast milk and may affect the infant. Among such drugs are the barbiturates. The whole problem of the excretion of abnormal substances in human milk has recently been reviewed by Illingworth (1953).

It is also well known that methaemoglobinaemia may occur in infancy through a variety of causes, including drugs taken by mouth, such as sulphonamides, ingestion of nitrates from well-water and the absorption through the skin of saline dyes used in ink to mark napkins. Methaemoglobinaemia may also be familial in origin.

The purpose of this paper is to present the case history of a newborn infant in which severe toxic symptoms occurred, consisting of drowsiness, anaemia, haemorrhages and methaemoglobinaemia. These symptoms were probably due to phenytoin (epanutin) and/or phenobarbitone taken by the mother during pregnancy and the puerperium. No reference has been found to cases of methaemoglobinaemia resulting from either of these drugs.

CASE HISTORY

A 5-day-old female infant was admitted to hospital on 23rd January, 1953 from a maternity home in a collapsed and profoundly anaemic state. She was the first infant of an epileptic mother. The mother had several major convulsions during pregnancy and was treated with a total daily dosage of 5 gr. (0·33 g.) of soluble phenobarbitone, 1 gr. (0·06 g.) of phenobarbitone in tablet form and 6 gr. (0·4 g.) of phenytoin (epanutin) both before the infant's birth and in the puerperium.

Labour was uneventful. The infant weighed 7 pounds 10 ounces (3,425 g.). She was stated to be blue at birth and was slow to breathe. She remained very sleepy during the first 4 days of her life, refused to suck and had to be fed by the mother's expressed breast milk and a complement of half cream National Dried Milk by means of a gastric tube. The infant vomited several times, the vomitus containing milk and mucus, but no blood. On the fourth day of her life her colour became very poor and she again vomited. Slight vaginal bleeding was noticed. On the morning of the fifth day she became extremely pale and collapsed. Bruising was noticed over her right ear and across her forehead. No other signs of bleeding were detected and the meconium was of normal colour. No abnormal signs had been found elsewhere prior to her admission to hospital.

On admission she was found to be extremely ill, collapsed and exsanguinated. Her pulse was imperceptible and her temperature was 99·6 F. (37·6 C.). There were large bruises over both ears and across the forehead and there was a little blue discoloration around the umbilicus. The liver was of normal size and the spleen was not felt. A normal stool was passed just after admission. She weighed 6 pounds 10 ounces (2,975 g.).

It was thought that the infant was suffering from haemorrhagic disease of the newborn, or from anaemia with a haemorrhagic tendency due to phenytoin and that the extreme drowsiness might be due to the large quantities of sedatives taken by the mother.

Unfortunately, it was impossible to make a complete haematological examination before transfusion. The infant was so collapsed that it was not possible to obtain more blood than was essential for cross matching, though strenuous efforts were made to do so. She was given 250 ml. of whole blood in the course of the next 48 hours. After this a blood count showed a haemoglobin of only 44 per cent (6·2 g. per cent), red blood cells 2·7 million per c.mm., white cells 22,000 per c.mm. (61 per cent polymorphs, 24 per cent lymphocytes, 9 per cent monocytes, and 2 per cent metamyelocytes); 3·5 per cent of the red cells were nucleated and there were 4·5 per cent reticulocytes. The platelet count was 230,000 per c.mm. As there was no further evidence of external or internal bleeding no further transfusion was given and the infant's haemoglobin rose steadily and satisfactorily to

74 per cent (10·4 g. per cent) on the 30th January, 1953, 7 days after admission.

The infant was fed on a donor's expressed breast milk, pending investigations of the drug content of the mother's milk. She improved steadily, took her feeds well within 24 hours and was alert. The mother's lactation was maintained by expressing her breast milk. Samples were sent to the public analyst for an assay of the phenytoin and barbiturate content. This, however, proved to be difficult and time-consuming, and the child was therefore put to the breast again on the 28th January, 1953. Within 24 hours she became intensely drowsy, refused to suck from the breast or from a bottle, and the mother's milk was given to her from a spoon. This drowsiness persisted and on 30th January, 1953 she was noticed to have a peculiar greyish-blue colour. Next day venous blood was taken for examination. The serum was brown in colour and on spectroscopic examination showed bands of methaemoglobin.

It was now decided to discontinue breast feeding altogether, and the child was established on a formula of National Dried Milk. She was also given 150 mg. ascorbic acid daily by mouth in three divided doses for 10 days. Her colour rapidly improved and after 2 days she became much more alert and remained so until her discharge from hospital. On 9th February, 1953 the colour of her serum had returned to normal and no methaemoglobin was detectable in it. Methaemoglobinaemia did not recur after discontinuation of ascorbic acid treatment. The blood count returned to normal and the child gained weight steadily, but had not regained her birth weight when discharged on the twenty-sixth day of her life.

Subsequent progress was uneventful and when she was last seen at the age of 7 months she was physically and mentally a normal infant with no evidence of anaemia or methaemoglobinaemia.

Comments

Unfortunately it was impossible to find an adequate method for the estimation of phenytoin in the breast milk and the makers also advised us that no method was available. Consequently the following conclusions cannot be considered to be proven.

It seems reasonable to assume that the two periods of intense drowsiness which coincided with the periods of feeding with the mother's milk were due to the excretion of sedatives in the milk and that the presence of excessive quantities of these drugs in the breast milk was also responsible for the production of the methaemoglobinaemia. Other known causes of methaemoglobinaemia have all been excluded.

Acknowledgments

We wish to thank Professor R. S. Illingworth for his criticism and to Messrs. Parke, Davis & Co. for their help with the literature of phenytoin.

Reference

Illingworth, R. S. (1953): *Practitioner*, **171**, 533.

CHARLES McINTOSH MARSHALL

Obituary

CHARLES McINTOSH MARSHALL

CHARLES MCINTOSH MARSHALL died on 21st September, 1954, at the early age of 53. By his passing British Obstetrics and Gynaecology in general and the Liverpool school in particular have lost, all too soon, an outstanding figure.

He was born in Invercargill, the most southerly city of New Zealand and was educated at Southland Boys High School and Otago University, Dunedin, New Zealand.

At school he was a classical scholar and showed two traits which flowered in later life in that he won prizes both for essays and languages. Literary ability was in the family for his elder brother, who predeceased him, was editor of the *Sydney Sun*. Charles's own writings were clearly, and often beautifully, expressed. At a comparatively late age he developed his linguistic ability in German to such a high degree that he was able to write and read papers in that language fluently and easily.

During his time at Otago University he showed a keen interest in Anatomy, an interest that remained with him all his life. His work throughout his course was of such a high order that he was appointed first junior house surgeon then senior house surgeon at his teaching unit in Dunedin and occupied the best posts, including those of house surgeon to the professor of surgery and to the professor of obstetrics and gynaecology.

He came to London with the aid of a Dominion Scholarship in 1926 and at once applied himself to increasing his surgical knowledge and reading for the F.R.C.S.

His early house appointments brought him under the influence of well-known men—E. T. C. Milligan at the Seamen's (Dreadnought) Hospital, Greenwich; Canney Ryall at All Saints Urological Hospital; many, but especially Victor Bonney, at the Freemason's Hospital and again at Chelsea Hospital for Women and J. Abernethy Willett at the City of London Maternity Hospital.

He became a Fellow of the Royal College of Surgeons, England in 1928.

The resident staff at the Liverpool Maternity Hospital was reorganized by Professor Leith Murray in 1932 and a post of resident obstetric assistant and registrar created. Charles Marshall was the first to hold this post. Three years later he was appointed to the consultant staff and then in 1943 to that of The Women's Hospital, Liverpool.

To say that he was now launched upon his career is an understatement for he had already made his mark, at least locally. Up to this time he had had his main opportunities in obstetrics and used them right well. He took much pains to ensure the success of the method of delivery of the after-coming head in breech presentation originally put forward by J. W. Burns so that the method has become known as the Burns–Marshall technique. It is due to his untiring efforts in instructing new members of the resident staff in this method—later supplemented by the application of forceps to the after-coming head—that the stillbirth rate at the Liverpool Maternity Hospital has been kept to such a low level.

His book *Caesarean Section, Lower Segment Operation* was published in 1939. In it he shows his love for anatomy, his care for and attention to detail and his scholarly ability as a writer.

Many other writings come from his pen but his great interest was in seeking ever better and safer means of relieving suffering women. His skill as an operator was a joy to behold and his demonstration of a particular technique a masterpiece of clarity.

He read obstetrical and gynaecological liter-

ature widely and critically and his knowledge was always at the disposal of anyone who sought it.

His work was equally well known in the United States of America and in Germany. Indeed he was much in demand overseas as a lecturer. He was twice invited to the U.S.A., one of these occasions being to give the Joseph Price Oration. Other invitations were to Cairo, Alexandria, Germany, Austria and Czechoslovakia.

Marshall was a keen and inspiring member of the Gynaecological Club. I was privileged to witness the esteem and affection in which he was held by his fellow members when the Club met in Liverpool in 1950.

His work, enlarged by his interest in the history of obstetrics and gynaecology, was also his hobby. To this he added a love of history in general so that reading historical works was his chief relaxation. At school he had enjoyed playing cricket and was no mean performer. He occasionally watched first-class matches in his later years.

Professor Jeffcoate has written such a beautiful account of Charles Marshall—the man—in the *British Medical Journal* (9th October, 1954) that any further attempt on that theme can only be imperfect.

Marshall was very reserved, indeed shy, and did not give himself easily in friendship. Once this reserve was overcome a most happy and cordial relationship blossomed. This trait was a part of his strong individualism which did not help him to fit easily into a team but, as in his personal relationship so in collective ones, when full confidence was established a happy and pleasant *modus vivendi* emerged. I am grateful that I was privileged to have him as a loyal and helpful colleague for a number of years.

The courage with which he faced his illness, fully knowing its inevitable end, was a source of deep admiration and indeed inspiration amongst those who were privileged to be included in the group he wanted to see. He frequently chose as a topic of conversation the future of the school, and the hospitals on whose staffs he had himself played such a brilliant part.

We extend our deepest sympathy to his widow, son and daughter.

ARTHUR A. GEMMELL.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

A MEETING of Council was held in the College House on Saturday, 27th November, 1954, with the President, Mr. Arthur A. Gemmell, in the Chair.

It was reported that a further gift of £5,000 from Mrs. Margaret Black to the Sims–Black Travelling Professorship Fund had been received.

The following awards were made for 1955:

Leverhulme Research Scholarships:

Professor I. Donald, Glasgow.
Dr. J. Gardiner, Bristol.
Dr. F. H. Leckie, Glasgow.
Dr. M. L. Paterson, Glasgow.

Bernhard Baron Travelling Scholarship:

Professor S. L. Townsend, Melbourne.

Green–Armytage Short Term Travelling Scholarship:

Dr. J. W. F. Scrimgeour, Manchester.

The Council acknowledged a further grant for research from the British Empire Cancer Campaign.

The following were admitted to the **Membership:**

Renu Kana Banerjee.
Kenakbeena Das Gupta.
William Griffith McBride.
Lachlan Hardy Wilson.

LIST of Candidates who have been awarded the **Diploma in Obstetrics:**

Mavis Jean Allanson.
Barbara Dorothy Allen.
Desmond Leslie Archer.
Robert Armatage.
William Macdonald Baird.
Cyril Edward Ballance.
Antony Pascal Barter.
Samuel Gregor Armson Bartlett.
David Arthur Vivian Bearblock.
William Morris Beatley.
Francis Xavier Bencini.
Bertram Ralph Arnim Binnewald.
Ethel Ada Lois Blake.
Ralph Anthony Timothy Boland.
John Malcolm Bolton.
George Michael Pearson Boyes.
Denys Spalding Neilans Brierley.
Robert Charles Brookes.
Thomas Brown.
Jennifer Browne.
James Chisholm Bryce.
Donald Budge.
Alexander Ramsay Burnett.
Margaret Helen Butler.
Arthur Paul Camilleri.
Kathleen Mary Carruthers.
Denis Cavanagh.
Alan Frederick Champion.
John Chapman.
Bina Chatterjee.
Herbert Donald Chomse.
Tuck Kwong Chong.
Agnes Clark.
Iain Macdonald Clark.
Alan Godfrey Clews.
Winifred Jean Coates.
Sheila Mary Cochrane.
Robert Lawson Kellock Colville.

Ellis Cooper.
Keith Coventry.
William Henry Andrew Chave Cox.
Albert Victor Craig.
David Ogilvie Craig.
Douglas Stuart Craig.
Anthony Allan Craigen.
David John Cross.
Lawrence Crouch.
Stuart Henry Dallas.
Duncan Dunn Davies.
Raymond Davis.
George Roger Clements Deacon.
Peter Alan De Raeve.
Ronald Frank Dingley.
Marjorie Jean Duckworth.
Sheila Grace Fullarton Duncan.
Ian Macdonald Duthie.
Austen Ernest Elliott.
Cathleen Mary Elliott.
Mary Alison Elsdale.
Lynn Anthony James Evans.
Noreen Marjorie Helen Evans.
Frank Hugh Evason.
Peter Grant Fildes.
Alfred Graham Findlay.
Anna Leonora Frenkiel.
Colin James Friendship.
Margaret Philomena Gardiner.
Nicholas Sefton Chamberlain Gent.
Arun Kumar Ghosh.
John Glover Ossett Gill.
Richard Michael Henry Gompertz.
Christoffel Jacobus Goosen.
Alistair Cameron Gow.
Dorothy Marian Gratton.
June Havergal Green.
Peter Joseph Guly.
Frances Mossley Wilson Hamilton.
John Noryl Harkness.
Norman Beesley Harris.
John Dudley Harte.
Charlotte Hartstein.
Kathleen Felizmina Hastings.
Deric Bjorkman Hawkins.
William Peter Hayne.
John Henry Heard.
Kenneth Reeve Heber.
Edward Richard Herst.
John MacLeavy Hill.
Barbara Mary Hitch.
Kenneth Spencer Holmes.
Edward Thomas Robert Holt.
Helena Everard Hughes.
Kenneth Rees Hughes.
Muriel Mallalieu Hughes.
Hubert Anthony Hurwood.
Jane Crossman Iles.
Alexander Ingram.
Doreen Laverock Ireland.
Edmund Percival James.
Gyanshila Jayaswal.
David Schofield Jeffery.
Alfred Howard John.
Martin Johnstone.
Robert Stevenson Johnstone.
David Rowland Jones.
Ellis William Parry Jones.
John Stuart Jones.
Richard Dean Jones.
Catharina Josina Joubert.
Paul Johannes Joubert.
Victoria Kathleen Kelly.
Dennis Murray Kirkwood.
Ethel Elizabeth Daunt Knowles.
Kenneth Barry Lazarus.
William Edward Lewis.
William Gwyn Lewis.
John Francis Lowe.
Samuel John Hyland Lowry.
Ian Barclay Lyon.
Iain Smith Macdonald.
Jean Munro Mackay.
Frances Evelyn Augustine McVey.
Doreen Elizabeth Mallagh.
Frank Dennis Marples.
Andrew Edward Bertie Matthews.
James Samuel Young Mathewson.
Mohammad Daoud Matuk.
James Ian Maxwell.
Bimla Mehra.
Victor Gordon Milne.
Derek Barnard Minton.
William Peter Lochrane Morrison.
Maureen Elizabeth Murphy.
Godfrey Thomas Nelson.
James Orde Newman.
Jean Johanna Salusbury Nicolson.
Harold Richard Hugh Noel Oaten.
John Fergus O'Keeffe.
Kenneth Leslie Oldershaw.
Joyce Elizabeth Anne Ovens.
Jack Palmer.
Michael Donovan Parker.
William Neil-Baron Parker.
Francis Ian Partington.
Myrtle Thelma Pateman.
John Hamilton Pauffley.
Charles Lynn Perry.
Laurence Arthur Pike.
Hyman Barend Polak.
Clare Elise Poundall.
Peter Horace Pullen.
Sheila Marshall Purchase.
Rajnikanta Puri.
Jenny Pym.
Norah Patricia Raitt.
Carmen Mary Rant.
Richard David Hamilton Reddy.
Barbara Anne Renwick.
Bruce William Richards.
Thomas Arthur Richards.

Colin Christopher Riley.
Theodore Michael Foulkes Roberts.
Malti Rohatgi.
Robert Anthony Rowan.
Albert William Russell.
Frank Wylam Russell.
Patrick Stanley Bruce Russell.
Annie Philomena Ryan.
Alice Laura Scott.
Joseph Henry Scudamore.
Muriel Joan Seaman.
David Anderson Seaton.
Adrian Murdoch Semmence.
Jean Mary Sharpe.
Graham David Hopper Shephard.
Hilary Joyce Shimmin.
Douglas Neil Sinclair.
William Nicol Sloan.
George Lindsay Smith.
Michael Arthur Smith.
Michael Glynne Smith.
Maurice Samuel Smyth.
Paul Berthon Sparke.
Robert Alexander Stark.
John Francis Stephen.
John Alexander Bannatyne Stewart.
Hugh Murray Strathern.
Pamela Mary Sutherland.
Peter Harrison Swinhoe.
Eva Susi Szmulewicz.
Elsie Gladys Taylor.
George Benjamin Taylor.
Patricia Irene Thomas.
Peter Riley Vernon Tomson.
Molly Ethel Towell.
Brian Arthur Tudgay.
Kathleen Dorothy Tulloh.
Michael George Skinner Vercoe.
Roy Walker Wallis.
Cynthia Margaret Ward.
Evelyn Dora Watkins.
Peter George Newall Watson.
John Leonard Weeks.
Kenneth John Stawell Whight.
Harry John White.
Ingeborg Ruth Wiernik.
Margaret Anne Wignall.
Samaraweera Mudalige Don George Robert Wijegunaratne.
David James Lloyd Williams.
Mary Alexandra Marshall Wilson.
Margaret Trafford Wood.
Joseph Herbert Woolf.
Dorothy May Wreford-Smith.
Frederic Robert Holland Wrigley.
Norman Young.

REPORTS OF SOCIETIES

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

JUNE 1954

A Meeting of the North of England Obstetrical and Gynaecological Society was held in the Royal Victoria Infirmary, Newcastle-upon-Tyne, on Friday, 4th June, 1954. The President, Dr. K. V. Bailey was in the Chair.

Mr. F. J. Burke and Dr. D. A. Leslie read a case record of

ADENOMATOID TUMOUR OF THE FALLOPIAN TUBE

(This article appears on page 817 of this issue)

Discussion. The President congratulated the speakers upon their excellent presentation of a case of extreme rarity. He regretted that time would not permit general discussion.

Mr. Frank Stabler read a paper on

DIFFICULTIES OF TREATMENT OF VAGINAL ATRESIA AND APLASIA

Mr. Stabler said that he had had 7 patients within the past few years showing varying degrees of genital aplasia and atresia other than the so-called imperforate hymen. They had shown a superfluity of complications and interesting difficulties.

If anything in the nature of a McIndoe vagino-plasty was being contemplated it should first be considered whether one could command the cooperation of the patient for the prolonged treatment necessary. One should not be too optimistic of the time it took to overcome the contraction of scar tissue. McIndoe's estimate of 6 months before the obturator could be discarded was the minimum time if everything went according to plan, and he started by telling his patients that it would be 12 months before treatment was completed. He would not attempt a McIndoe reconstruction in an excitable impatient type of woman.

His first patient was one with complete Müllerian aplasia who was of an excitable, self-willed type and, when she refused a McIndoe reconstruction, he did not press the matter. She was nursemaid to a physician and, in his household, maintained a pantomime of menstruation. She married in spite of the absence of a vagina and some time later went on holiday for a month, after which she returned with a baby, and even to her former mistress claimed that she had been delivered of this child.

His second patient was perfect in this respect and was what is described in modern idiom as "Dumb". She got the most perfect result.

Helen, who had presented with primary amenorrhoea at the age of 26 years, did not have an intravenous pyelogram. He thought that, as she did appear to have a uterus, she was likely to have an upper end of vagina. He contemplated a modified McIndoe operation, but decided to make a channel from above down and opened her abdomen. There was one ovary, the right, with one inch of Fallopian tube and a gubernaculum. The object which he had taken to be the uterus was a pelvic kidney on the right side, and there was no left kidney. The abdomen was closed, and 16 months later, she was admitted to hospital with renal tetany. The associated renal malformation may, therefore, be of serious importance.

Previous Treatment. Two patients had had previous treatment and in each case serious harm had been done. Maureen had a uterus didelphys with double vagina with atresia of the lower portion of the right vagina, and as a case of suspected appendicitis with a normal menstrual history she came under the care of a general surgeon, who found a tense fluctuant mass in the pelvis and passed a needle into it through the rectum. He retrieved dark menstrual blood, but also infected the collection and, 6 days later, when it was drained per vaginam, it was foul smelling. A fortnight later still Mr. Stabler had to open the abdomen and remove an infected haematosalpinx.

Joan was a pleasant but somewhat mentally retarded girl of 20 years. The parents were neglectful and dirty. Because of urinary incontinence they kept the girl in a dark kitchen like an animal. Four years before she had gone to another hospital with primary amenorrhoea and recurring pain in the abdomen. An operator had started to make an opening from the vulva but, finding himself in difficulties, stopped. Ever since this operation the patient had had incontinence of urine. He was later said to have done a hysterectomy, but when Mr. Stabler examined rectally he felt what seemed to be a well-formed uterus. Three years later and three months before he saw her a fascial sling operation had been done. No benefit accrued and it was planned that the ureters should be transplanted. Her doctor referred her to Mr. Stabler, who found the urethral floor had been laid open to the bladder trigone. He carried out a colporrhaphy or urethro-plasty, but incontinence returned. Three months later he tried again and carried out a wider dissection around the urethra and kept the patient in bed for nearly 3 weeks. She had been perfectly continent since.

The operation. In doing McIndoe's operation it should be remembered that in the absence of a vagina the rectum was in contact with the urethra. The external conformation of the vulva in his cases had been normal with a hymen and perineal fourchette sketched out on the surface. The rectum lay in the perineal body above the level of this fourchette.

At least three moulds of different sizes should be made ready and if the mould was slightly enlarged at its upper end it would be less likely to come out. If it was too bulbous it might be retained. He had not yet succeeded in stitching in a mould and getting healing over it. In each

case the stitches had cut through and the obturator had tended to extrude. A cup and stem pessary with the stem cut off could be used as a platform to hold the mould in place. He had found that Paget's dermatome was very satisfactory in use and, with it, he himself had cut a perfect graft 9 by 4 inches. He had first practised on dead bodies.

Barbara had atresia of the lower 1½ inches of the vagina, but had a normal uterus and vaginal vault save for haematocolpos and haematometra. He drained these and set about fashioning a vagina. He had left a canal through the obturator for the passage of menstruum, but infection followed and, in spite of severe tubal infection, the obturator had to stay in position. As a graft it was a success for there was an epithelium lined canal, but as an operation it was a failure for he was sure that he would eventually have to remove both tubes and he had hoped to get a functioning genital tract.

In Winifred's case all the graft "took" except for a penny-sized area on the anterior vaginal wall, possibly due to the filling and emptying of the bladder. He put silkworm stitches all around the raw area and left one end long. He then applied a graft, and built up a haycock of cotton wool over it. The graft "took" in 10 days and there was no deformity.

Elizabeth too got a penny-sized raw area on the anterior vaginal wall. The plastic surgeon advised that it should be left alone to epithelialize over. It did, after months, but produced a stricture so that now only a 2-inch long vagina was available.

The Lesion. The last difficulty might be in defining the lesion. Sheila was 16 and menstruation had been normal since the age of 12 years. Suddenly she had a profuse discharge of thick tarry material and, when he told the mother that she must have a double uterus, she told him that the grandmother had had a double uterus. He advised allowing the menstruum to discharge naturally and 10 days later he was recalled because the discharge had become foul. On examination under anaesthesia the vagina appeared to be clean and healthy with a single cervix. He advised douches and antibiotics, but after 6 months the very offensive discharge was still present. He again examined under anaesthesia and a gush of foetid pus came down the vagina. He then decided that there must be a uterus bicornis unicollis and hoped that the pyometra was one sided. He opened her abdomen and found the left uterus and tube showing signs of old blood distension and removed them, but the foul discharge persisted. Ten months after the original consultation, on speculum examination he found the pus exuding from a minute puncture in the left fornix. On opening it the hitherto hidden left upper vagina full of pus was revealed. He removed the septum and there had been no further trouble.

Name and Age	Genitalia	Renal Tract	Mentality	Previous Treatment	Treatment	Subsequent Progress	Result
Helen 26	Right ovary and gubernaculum only.	One kidney only. Sacral in position.	Self-willed. Fantasies.	Nil.	Laparotomy.	Renal tetany.	In statu quo.
Winifred 25	Apparently complete Müllerian agenesis.	Normal.	"Dumb."	Nil.	McIndoe.	Graft to anterior vaginal wall.	Good.
Barbara 15	Atresia of lower half of vagina. Haematocolpos and haematometra.	Right kidney normal. Left kidney situated over sacro-iliac joint.	Normal.	Nil.	Modified McIndoe.	Severe pelvic infection.	Still being treated. Not good.
Joan 20	Doubtful.	Right kidney duplex. Single ureter. Left kidney duplex. Double ureter.	Retarded.	1. Attempt McIndoe. 2. Hysterectomy. 3. Fascial sling.	Urethro-plasty.	Urethro-plasty.	Continence.
Elizabeth 18	Apparently complete Müllerian agenesis.	Normal.	Normal.	Nil.	McIndoe.	Scarring of anterior vaginal wall.	Half size vagina. Function satisfactory.
Sheila 16	Uterus didelphys and double vagina. Atresia lower half of left vagina with haematocolpos and haematometra.	Right normal. Left absent.	Intelligent.	Spontaneous opening.	1. Douches. 2. Left sub-total hemi-hysterectomy. 3. Removal of septum.		Good.
Maureen 16	Uterus didelphys and double vagina. Atresia lower half of right vagina with haematocolpos and haematometra.	Right absent. Left normal.	Normal.	Rectal exploration. Infection.	Removal of septum.	Right salpingo-oöphorectomy.	Good.

Discussion

Dr. Bailey thanked Mr. Stabler for his interesting account of his personal experiences in dealing with what were rare conditions.

Professor Bruce Mayes (Sydney, Australia) read by invitation a paper on

Anuria

Professor Mayes said that the term "anuria" was not always accurate; it might be severe oliguria, in which case the prognosis was somewhat better. There had been 5 obstetric cases of anuria in ten years in 32,963 deliveries at the King George V Hospital, Sydney. They had followed severe toxaemia, accidental haemorrhage and abortion. He doubted whether any problem was approached with greater uncertainty of the result, in spite of a most strenuous and conscientious effort. He thought the most practical way to consider this condition would be to discuss 2 cases, both of which recovered.

The first was in 1943; the pregnancy was terminated vaginally at 6-months gestation for a severe toxaemia, probably nephritic. He would never attempt a vaginal delivery at 6-months pregnancy again—but would do a hysterotomy. The strain of 2 days delay following an attempt at vaginal delivery was too much for a woman who was sick enough to have her pregnancy terminated. Anuria occurred and the blood urea rose to high levels, but diuresis was progressively re-established and after 8 days reached a reasonable figure. The woman was fed purely on intravenous glucose—500 ml. of 25 per cent glucose in distilled water intravenously every 8 hours for 24 hours, and thereafter 12 hourly for 4 days. She had a high blood sugar on 3 successive days, as might be expected.

The second case, in 1950, was of a patient aged 36, who had eclampsia and accidental haemorrhage. She was delivered of a stillborn baby 32 hours after admission, and in the next 24 hours passed only ½ ounce of urine which was solid with albumen. For 5 days she was extremely ill—a typical uraemic case. Interestingly, although her condition then improved with the output of urine, the blood urea continued to rise. Treatment was by continuous intragastric drip along the lines recommended by Bull, a litre of the emulsion of 400 g. glucose, 100 g. peanut oil, in acacia and water being given daily.

The woman was pale, an important factor in these sick patients. The haemoglobin fell considerably in the first couple of days and she was given a transfusion of packed red cells. The improvement in her renal condition coincided with the improvement in her blood stream. It was reasonable to expect that poorly-functioning kidneys would have a better chance of recovering if they were bathed by a good blood stream.

The term "anuria", Professor Mayes continued, was used loosely and in many cases which recovered the anuria was perhaps not complete. While a woman was passing even a drachm or two of urine, it indicated that some renal tissue was capable of doing some work and if the patient could be kept alive for a number of days she might recover. But where there was no urine secreted at all it was very difficult to conclude that the patient's renal function was not completely destroyed.

With regard to treatment, both successful cases described seemed to have one factor in common and that was the intravenous glucose. It not only provided food which kept the patient alive, but also reduced the breakdown of endogenous protein and reduced the concentration of potassium in the extra-cellular fluids. It had been known for some time that potassium was a serious factor in cases of shock, and it was essential to keep the potassium level at a normal or lower than normal figure. The normal range of the blood potassium was 18–22 mg. per cent. In the second case, although it was above the upper level of normality to start with, it fell and thereafter was kept at a satisfactory level. In both cases the protein element was kept at a minimum. This may have kept the blood urea from rising to astronomic heights but he doubted whether this was of supreme importance. It was not the urea but probably other substances which constituted the toxic agent in uraemia.

One point which was elementary but vital was good nursing. For example, treatment by intragastric drip sounded simple, but it needed a cooperative patient and a first-class nurse. In a debilitated patient a great deal of expert nursing was needed, attention to pressure areas and to the mouth which was not functioning and so on. Another important factor was the warmth of the patient, while reassurance by an understanding nurse could do a lot of good. Last, but not least, there was sleep or rest. With the frequency of ministration of so many therapeutic drugs today he wondered whether the patient could get enough sleep. In 1863, one John Hylton published a little book called *Rest and Pain*. He said "Rest is essential to growth; we recognize this in the growing child; the one who sleeps most, usually thrives. What is true of growth is also true of repair. Repair is but the repetition of growth."

There were other methods of treating anuria, such as peritoneal lavage, of which he had had no experience, and the artificial kidney. Their greatest success had so far been with the glucose and peanut oil, and he was appreciative of the help and courtesy he had received from Professor Bull of Belfast.

In summary, said Professor Mayes, he could not exclude the feeling that whatever method had been used, all that they could claim was that they had kept some patients alive by good nursing and artificial feeding for some days. He regarded the obstetric cases as having a better outlook than cases of anuria in other patients, because the termination of pregnancy might be a positive factor for good. Although most cases of anuria occurred *after* delivery, the fast demobilization of the forces of the body which followed confinement might constitute a lessening of the strain under which the sick body was functioning. This factor did not exist in other cases of anuria.

With regard to the question of whether a woman who had had obstetric anuria should be discouraged from further childbearing, the subsequent history of the second patient was of interest. She was only 26 years of age, and

determined to have a live baby. She attended again, conception having taken place 11 months after the near-tragedy of the first. In her second pregnancy the only thing that worried her was blurring of vision when reading or sewing. She was admitted to hospital for investigation with a blood pressure of 160/110 but this settled down after rest for 2 weeks to 130/90. There was no albuminuria or oedema. Her blood urea was 38 mg. per cent and urea concentration tests showed that she concentrated to 2·5 per cent, but it was his opinion that the urea concentration test in pregnancy was of very little help. The patient was readmitted at 37 weeks when her blood pressure was 160/110 and oedema and albuminuria were marked. The blood urea was then 60 mg. per cent. Labour was induced by stripping the membranes and she gave birth to a living baby weighing 7 pounds 3 ounces. She did not repeat her anuric story but had an uneventful puerperium.

As scientists, concluded Professor Mayes, we might be inclined to shake our heads and say, "Pregnancy was not intended for the likes of her and having babies will shorten her life". But as a practising obstetrician he felt that it was difficult in every case to reduce obstetrics to a purely scientific subject; the human factor sometimes took charge and who would challenge a woman's philosophy that she had only one life to live and even if short, it should be a full one.

The President thanked Professor Mayes for his excellent paper, which Professor A. M. Claye said had been eminently practical.

SOCIETY FOR THE STUDY OF FERTILITY

The Annual Conference of this Society will be held in the Large Anatomy Lecture Theatre of the Medical School, Hospitals Centre, Birmingham, on Thursday and Friday, 23rd and 24th June, 1955.

Further details of the Conference and Social Functions may be obtained from the Honorary Secretary, Mr. H. H. Fouracre Barns, at 31 Weymouth Street, Portland Place, London, W.1.

BOOK REVIEWS

"Reproduction and Sex." By G. I. M. SWYER, M.A., D.M., D.Phil., M.R.C.P. Pp. viii+280. Illustrated. Routledge & Kegan Paul, Ltd., London, 1954. Price 25*s*.

THIS is the second book of a series on various aspects of human biology. Those books are addressed to "those who take a serious interest in human affairs, ... specialists in a variety of professions, and students . . ., in the main fields of biology". Beginning with anatomical and physiological descriptions of the reproductive tract the author then discusses conception, pregnancy and labour.

This is followed by a first-class discussion on fertility, infertility and contraception; the professional experience of the author contributing greatly to the value of those chapters. The later part of the book, a discussion of normal and abnormal sex behaviour draws heavily on the experience and writings of Dr. A. C. Kinsey and his colleagues.

The chapters dealing with problems of abnormal pregnancy and labour are somewhat old fashioned and, rather than being simple and explanatory to the intelligent lay reader, over-emphasize the abnormal and highlight the "hazards".

It is extremely difficult to write a text which will stimulate the intelligent layman with clear but non-technical description and satisfy the trained biologist with detailed information in a field which is not his own. This book has much to offer the reader but it is a great pity that it was not designed and written exclusively for the intelligent layman. Technical phrases and rather poor diagrams could then have been replaced by accurate but simple descriptions and line drawings. Despite an extensive glossary many of the technical descriptions will be completely unintelligible to the untrained.

James Walker

"Practical Obstetrics." By BRUCE T. MAYES, *M.V.O.*, F.R.C.S.E., F.R.A.C.S., F.R.C.O.G., Professor of Obstetrics, University of Sydney. 2nd Edition. Pp. xv+500, with 181 figs. and 15 plates. Angus and Robertson, Sydney and London, 1954. Price 87*s*. 6*d*.

DR. BRUCE MAYES made many new friends during his recent visit to Britain as Sims-Black Commonwealth Travelling Professor. Among those who did not meet him in person, this book will win many more friends for him, for his personality and temperament come to life in its pages, in which in effect he has transferred the teaching clinical ward round to print. The content is practical without shunning all academic knowledge, and the style is graphic without being overdrawn. The illustrations are excellent and the production falls from grace only in the incorrect paging in the list of contents of Chapter 21.

In most of the 38 chapters the author deals with a practical obstetric problem, citing typical cases and discussing diagnosis and treatment with special emphasis on the difficulties that may be met. Throughout the whole book run the themes that judgment is not always easy and that many problems have no certain and constant solution. The few chapters on sterility and allied subjects seem somewhat out of place and might be omitted from the next edition. In them the mis-statement that oestrogen raises and progesterone lowers body temperature has been overlooked (p. 446).

Professor Mayes writes so charmingly, so wisely and with such balance that criticism is almost disarmed; almost, but not entirely. In the case illustrating the Rh factor in pregnancy, it is first stated that the second baby lived although lightly jaundiced for a few days. Later it is added that this baby was Rh-negative, yet the mother was regarded as fortunate not to lose it. On the contrary, she might be regarded as unfortunate in losing the third baby with hydrops foetalis for, on the facts given, the father must have been heterozygous Rh-positive. In this volume conservatism is generally and rightly advocated but it might be considered tempting fate to allow a woman with a big breech baby to go 5 weeks past her expected date of labour; and a successful outcome in such a case should not "give you confidence" (p. 489). The value of abdominal paracentesis in the treatment of some cases of hydramnios is worthy of mention. The author appears to have more faith than most in the efficacy of hormone therapy, particularly in the value of stilboestrol in the prevention and treatment of inertia. At the same time he plainly shows that his is no closed mind; infallibility is not claimed and dogmatism is eschewed.

The merits of this book will gain it a deserved popularity. Among the lessons preached perhaps the most impressive are the reiteration that more is missed by not looking than by not knowing; the emphasis on the value of intranatal radiography; and the reminders that the individual obstetrician must allow limitations of personal experience and of facilities to modify his management of any case. As with all records of personal views and experiences, the reader may not find himself in agreement with points of practice, such as the advocacy of axis-traction forceps, or of theory, such as the aphorism that a short labour is a safeguard against post-partum haemorrhage. But one has the impression that Professor Mayes enjoyed writing this book—and is looking forward to enjoying any criticisms of it. For although his main object has been to place his extensive experience at the service of the less-seasoned obstetrician he has also striven to stimulate thought and discussion. He has succeeded in both respects, and in the process he has given an admirable exposition of two arts, the art of obstetrics and the art of teaching.

REVIEW OF CURRENT LITERATURE

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ANATOMY AND PHYSIOLOGY

261. Observations on the Interstitial Portion of the Fallopian Tube.

By J. R. Lisa, J. D. Gioia and I. C. Rubin. *Surg. Gynec. Obstet.*, **99**, 159–169. Aug. 1954. 16 figs. 8 refs.

This report from New York follows the study of 300 uteri obtained from 259 hysterectomies and 41 autopsies. The total number of tubes successfully sectioned was 554.

In 65 cases the uterine body was free of changes which could cause pathological distortion of the interstitial segment of the Fallopian tube. In 65 cases uterine fibroids were present. In 59 cases the uterus was involved with adenomyosis and in 111 cases both fibroids and adenomyosis of the uterus were noted.

The interstitial segment is judged to be 1 cm. or less in length. The shape is that of a cone. The tip of the cone fuses with the cornual part of the extra-mural tube and the proximal part with the myometrium.

The interstitial segment of the tube has two components, a muscular coat and mucosa. The muscle has two layers, an outer circular and an inner longitudinal layer. The mucosa is characterized by a single-layered columnar epithelium and a villous pattern. The villous pattern is present at all ages and is extremely variable in appearance. It may be very simple or may be so complex as to resemble the ampulla. At the interstitial ostium there is usually an abrupt change between the endometrium and the tubal epithelium. Occasionally there is a gradual transition making it difficult to draw a sharp line of transition between the tube and the funnel of the uterine cavity.

Endometrium was present in the mucosa of the interstitial segment in 25 per cent of the entire series. Cicatricial atresia from inflammatory disease was found in 4 instances and in 1 other the atresia was due to a small adjacent fibroid. Stenosis was uncommon and was generally caused by polyps originating from the mucosa. Polyps were present in the tube in 11 per cent of the series. They were always endometrial and arose from isolated endometrial foci. There was a solitary instance of papilloma and one of primary non-invasive carcinoma in the interstitial portion of the tube.

The authors discuss the significance of endometrium in the interstitial portion of the tube. They consider that this is a normal developmental phenomenon and is not *per se* a pathological condition. Its presence does not appear to

play an appreciable role in the production of infertility and it has no definite causal relation to extra-uterine endometriosis or salpingitis isthmica nodosa.

John P. Erskine

262. **Meiosis and Fertilization Studies of Mammalian Ova in vivo and in vitro.** (Méiose et fécondation, Étude in vivo et in vitro sur l'ovule des mammifères.)

By R. MORICARD, *Gynaecologia, Basel*, **138**, 310–336. Aug. 1954. 5 figs. Bibliography.

This beautifully illustrated paper embodies the important work done by Moricard in the field of the study of mammalian ova.

Fertilization is defined as the union of a spermatozoon and an ovum. Meiosis is the formation of 4 haploid cells, i.e., one ovocyte or one spermatid and three polar bodies. Thus fertilization may be defined as the union of two haploid cells, containing the chromosomes of maternal and paternal origin, with the restoration of the original number of chromosomes.

In hypophysectomized animals there is a regression of ovarian weight with a total arrest of secretion of liquor folliculi. This change can be reversed by injection of anterior pituitary extracts.

In the rabbit division of the tetrads may be provoked by intravenous injection of gonadotrophin or by coitus. Injection of 0·00005 International Units of gonadotrophin provokes the metaphase with emission of the first polar body.

The author next describes his observations made *in vivo* on fertilization in the rabbit. The sperm and the ovum reach maturity, and thus are ready to achieve fertilization at about the same time.

It is impossible to achieve fertilization *in vitro* using ovocytes obtained from the ovary or from the tube and suspended in physiological saline and adding sperms obtained from the ductus deferens. It is found that these sperms cannot penetrate the zona pellucida. Some substance present in the tubal secretion is necessary to attract the sperms. Fertilization *in vitro* is however possible if the ovocyte is cultured in fragments of tube and the sperms are taken from the vagina after coitus. In this case, the sperm penetrates into the ovum but without the formation of pronuclei.

If newly-shed rabbit ova, obtained 10 hours after coitus, are cultured in uterine secretions containing spermatozoa, fertilization occurs with formation of pronuclei. The utero-tubal secretions thus play an essential part in fertilization and the development of the mammalian ovum.

It is suggested that these observations should be applied to the study of the maturation and fertilization of the human ovum.

Josephine Barnes

263. **Time of Ovulation in the Menstrual Cycle.** (Tiempo de ovulación en el ciclo menstrual.)

By R. PINEDA, P. BORRAS and G. CAMPAGNOLI *Obstet. Ginec. Lat.-amer.*, **12**, 126–129. Mar./Apr. 1954. 6 refs.

The authors report a study of time of ovulation by direct examination of the ovaries in a series of 268 laparotomies, performed on patients for other than gynaecological conditions—e.g., appendicitis, etc. Every patient at the time of the examination was between the 5th and 26th days of the cycle, and had stated that she had normal menses.

To interpret their findings, the authors stipulated that (1) a mature follicle would be presumed to rupture in 24 to 48 hours, and (2) a freshly ruptured follicle was presumed to have ruptured during the previous 24 hours. In a series of 84 such cases, it was estimated that the follicle had ruptured or was about to rupture in

26 cases between the 5th and 10th day, in
53 cases between the 11th and 19th day, and in
5 cases between the 20th and 26th days.

A vascularized corpus luteum was found in 150 cases at the following times:

10 between the 5th and 10th day (7 on the 9th–10th day).
122 between the 11th and 19th day (50 on the 17th–18th day).
18 between the 20th and 26th day (7 on the 20th day).

By subtracting 72 hours in each case, it was estimated that ovulation had occurred in 135 cases (90 per cent) between the 8th and 19th days, 87 of these (58 per cent) being between the 13th and 16th days. Combining these two series (234 ovulations), it was estimated that 128 cases ovulated between the 13th and 16th days.

In 83 of these cases, the endometrium was examined also, and the authors found that in cases where the follicle had not ruptured, secretory changes were present in the endometrium nevertheless. They also found that destruction of a corpus luteum, or even the taking of a biopsy from it, always caused a uterine bleeding. On the other hand, puncture of a follicle caused no bleeding.

In 87 cases of known ovulation, biopsies of the endometrium were taken at the onset of menstruation, and in each case secretory changes were found.

The authors conclude by stating that if the menstrual rhythm is normal (i.e., 3–4/28), ovulation occurs between the 8th and 19th days in 85 per cent of cases, and between the 13th and 16th days in 55 per cent of them. They regard the Basal Temperature recording method as a reliable sign of ovulation, judging from their observations in this series.

John F. Foulkes

OBSTETRICS

264. **Obstetrics Today and Yesterday.**

By L. TOWNSEND. *Med. J. Aust.*, **2**, 377–383. Sept. 4, 1954.

A comparison is made of statistics for 1943 and those for 1953 firstly from The Women's Hospital, Melbourne, and secondly from the State of Victoria.

At The Women's Hospital there was a reduction in the number of maternal deaths per 1,000 from 1·85 among booked cases in 1943 to 0·32 in 1953, and in emergency cases from 23·5 to 6·0.

The number of deaths shows a reduction in toxaemias from 9 to 2, in rupture of the uterus from 3 to 0, in post-partum haemorrhage from 2 to 0, and in puerperal infection from 3 to 0.

The reduction in maternal mortality from toxaemia has been due to stricter control and supervision of patients with insistence on regular attendance at the antenatal clinic, the control of weight, and detailed dietetic control.

The reduction in the mortality rate from rupture of the uterus has been made possible by greater availability of blood, by modern anaesthesia and by chemotherapy.

The incidence of Caesarean section has risen from 1·91 to 2·69 per cent. In 1943 20 per cent of all Caesarean sections were of the classical type and in 1953 only 4 per cent.

The total foetal death rate following Caesarean section fell from 21·9 to 12·6 per cent. In repeat Caesarean sections in 1953 the neonatal death rate was 7·2 per cent. In 1943 the incidence of post-partum haemorrhage was 11 per cent with 2 maternal deaths and in 1953 2·2 per cent with no maternal deaths. This has in the main been accomplished by the use of intravenous ergometrine before delivery of the placenta. With the routine use of ergometrine in this way the number of cases of retained placenta has increased.

Puerperal bacterial infection has greatly decreased. In 1943 the morbidity rate was 8·9 per cent and there were 5 deaths among 3,341 confinements while in 1953 the morbidity rate was 1·5 per cent and there were no deaths among 6,802 confinements. The major bacterial cause of puerperal infection was the anaerobic streptococcus.

In the State of Victoria the maternal death rate fell from 3·48 per 1,000 in 1943 to 0·62 per 1,000 in 1953, and the foetal death rate from 87 to 36 per 1,000. The stillbirth and neonatal death rates per 1,000 fell from 52 to 20 and from 35 to 16 respectively.

S. Devenish Meares

265. **The Epidemiological Approach in Obstetrics.**

By D. BAIRD and A. M. THOMSON. *Gynaecologia, Basel*, **138**, 226–245. Aug. 1954. 7 figs. 18 refs.

The authors stress the value of an epidemiological approach to the study of obstetrical problems.

The methods of analysis of obstetric cases are described. Abortions are excluded and so are multiple births as the latter present special problems. In general cases are divided into legitimate and illegitimate births and into booked and emergency cases. Biological classification is then possible. The factors taken into account are age, parity, social status, physique and general health.

As an illustration of the use of this method the results of study of gestation period are given. These show a sharp rise in foetal deaths due to obstetric causes when pregnancy exceeds one week past term (280 days from the last menstrual period). As a result it has become the policy to induce labour in all cases where pregnancy is prolonged to one week past term. The reasons for difficult labours and Caesarean sections have also been analyzed and a suitable classification of stillbirths and neonatal deaths on clinical grounds has been evolved.

This approach has been found to raise the standards of clinical records and to assist in the planning of laboratory research. It also provides a means of studying biological and social trends in mortality and morbidity and thus suggests means of reducing these.

Josephine Barnes

PREGNANCY

266. **Cardiovascular Physiology in Normal Pregnancy: Studies with the Dye Dilution Technique.**

By J. Q. ADAMS. *Amer. J. Obstet. Gynec.*, **67**, 741–759. Apr. 1954. 4 tables. 4 figs. 41 refs.

The author has used a new method for determination of cardiac output and plasma volume based on the Hamilton dilution principle which allows repeated estimations to be made on the same patient with little discomfort. He made 94 determinations on 31 normal pregnant women at intervals of 4 to 5 weeks, and also in the puerperium. The cardiac output was found to rise rapidly from the 12th week to a maximum at 28 weeks, when it is 32 per cent above the levels in non-pregnant controls. After that it decreases and reaches the non-pregnant level at 38–40 weeks. Immediately after delivery there is another rapid increase of 29 per cent, but by the second week after delivery it has again fallen to the non-pregnant level. The plasma volume rises in normal pregnancy but more slowly than cardiac output, and the maximum is reached at 32–34 weeks when the increase amounts to 22 per cent. It does not decrease significantly in the last trimester. The red cell volume increases in pregnancy but to a much less extent, hence the haemodilution of normal pregnancy, which is greatest at the point of maximum plasma volume. In normal pregnancy the total peripheral resistance and mean blood pressure decrease, and reach their lowest level at the point of maximum cardiac output. This decrease is probably due to the enlarged maternal sinuses, the arterio-venous placental shunt, the increased cardiac output and the decreased viscosity of the blood.

F. J. Browne

267. **Diagnosis of Early Pregnancy by Cervical Mucus Smears.**

By L. D. SPRAGUE. *Obstet. Gynec.*, **4**, 117–121. July 1954. 5 figs. 6 refs.

Roland (*Amer. J. Obstet. Gynec.*, **63**, 81, 1952) suggested that cervical mucus smears were of value in the early diagnosis of pregnancy. This study confirms that opinion. Smears are collected from the cervix and spread on a glass slide. They are allowed to dry and then examined under the microscope for fern formation (a blue glass filter is useful). The accuracy of this test approached 99 per cent in 900 slides studied. Five per cent of the slides taken in the first month of gestation showed atypical crystallization which must be differentiated from the true fern pattern.

J. G. Dumoulin

268. The Results of Increased Consumption of Fibrinogen in Obstetrics. (Syndromes aigus consécutifs à une consommation accrue du Fibrinogène en obstétrique.)

By R. MASURE and J. A. SCHOCKAERT. *Gynaecologia, Basel*, **138**, 75–86. July 1954. 27 refs.

Studies of blood coagulation were made in 6 cases of premature separation of the normally situated placenta and in 1 case after evacuation of a dead foetus.

In 5 cases hypofibrinogenaemia was found. In 4 of these this was accompanied by prolonged prothrombin and thrombin times. In 2 cases the heparin test revealed hypo-coagulability. In spite of this only 1 case showed a tendency to haemorrhage. No evidence was found of abnormal fibrinolytic or fibrinogenolytic activity.

The retroplacental blood studied in 2 cases showed marked coagulant power but with no evidence of anti-coagulant or lytic activity. The hypofibrinogenaemia is apparently related to this.

It is believed that the lengthening of the prothrombin time is related to the presence of a substance with anti-thrombin activity.

The implication of these observations in the management of obstetrical emergencies is discussed. In the cases where grave disturbances of coagulability persist the performance of emergency hysterectomy must be considered.

Josephine Barnes

269. Serum Antithrombin Content in Pregnancy.

By J. C. W. MACFARLANE and A. P. NORMAN. *Brit. med. J.*, **2**, 573–574. Sept. 4, 1954. 2 figs. 2 refs.

The authors, having found unexpectedly a low serum antithrombin level in a pregnant woman, while investigating patients with coeliac disease, undertook an investigation of the levels in women in pregnancy and the puerperium, and in newborn infants. All mothers and babies were healthy. The test consists of the incubation in a water-bath at 37° C. of a standard solution of thrombin mixed with the serum to be tested, and the timing of the clotting of standard amounts of normal citrated plasma by this thrombin-serum mixture after 5, 10, 15 and 20 minutes' incubation. The clotting times of each sample are expressed as a percentage of those obtained using normal serum as a control. In the assessment of results, only the 20-minute sample was used, as in this sample any deviation from the normal was most marked.

Sera were obtained from 120 women whose pregnancy varied from 4 weeks to full time; from 41 women delivered from 1 to 12 weeks previously; from cord blood at 30 births; and from 15 babies aged 1 to 14 days. Results showed that by the fourth week of pregnancy the level dropped to 67 per cent of normal, with steady further drop during pregnancy, with levels near term of about 35 per cent. Somewhere between 5 and 8 weeks post-partum the results returned to normal.

Sera obtained from cord blood gave a mean level of 32 per cent of normal.

The authors offer some suggestions as to the causation of these abnormally low levels in pregnancy. They also suggest the test as a useful aid to diagnosis of pregnancy.

Eileen Wilson

270. Intravascular Clotting and Afibrinogenemia, the Presumptive Lethal Factors in the Syndrome of Amniotic Fluid Embolism.

By D. E. REID, A. E. WEINER and C. C. ROBY. *Amer. J. Obstet. Gynec.*, **66**, 465–474. Sept. 1953. 1 fig. 19 refs.

In 1941 Steiner and Lushbaugh (*J. Amer. med. Ass.*, **117**, 1245, 1340) claimed that amniotic fluid embolism could obstruct the pulmonary arterioles and cause fatal shock during labour, while in those who survived there might be haemorrhagic manifestations. At the Boston Lying-In Hospital evidence was obtained that liquor amnii contained a substance that behaved like thromboplastin and could reduce clotting time in haemophilic blood. This suggested that death in this syndrome would be due to other causes than mechanical blockage by amniotic fluid debris, such as intravascular clotting or subsequent post-partum haemorrhage due to afibrinogenaemia, the end result of extreme intravascular clotting. The absence of extensive intravascular clotting and the fluidity of the blood found at post-mortem examination on one patient who had had amniotic fluid em... and died of uncontrollable post-partum haemorrhage are believed to be due to the effect of a fibrinolytic enzyme which can be demonstrated in the blood after sudden death. In the absence of a blood fibrinogen concentration necessary for effective haemostasis (100–150 mg. per cent or more) clot formation at the placental site would be deficient and fatal post-partum bleeding would occur. Six cases are cited in support of this concept. In the first labour was induced by giving 1 minim of pitocin intramuscularly and tumultuous labour ensued immediately. After 2 hours the patient collapsed, became unconscious and stopped breathing. Stimulants and artificial respiration restored her and a dead child was born. Soon after delivery she began to bleed *per vaginam* and this persisted though uterus and vagina were packed. The episiotomy wound bled freely, ecchymoses appeared all over the body, and it was noticed that the blood failed to clot. Transfusion of 6,000 ml. of whole blood was given over 15 hours but the fibrinogen concentration after its completion was only 134 mg. per cent in contrast to a normal value in pregnancy of over 300 mg. Five g. of fibrinogen were infused and after this the bleeding ceased. Clot formation of venous blood was normal, and blood drawn 2 hours later had a fibrinogen concentration of 450 mg. per cent. Recovery was uninterrupted. The other cases did not differ in any essential particular. Premature rupture of membranes, vigorous labour, cyanosis and anoxic convulsions form the typical sequence of events. If the patient survives the initial shock uncontrollable post-partum haemorrhage ensues.

It has long been known that if a near pure preparation of thromboplastin is infused rapidly intravenously death soon follows, but if given slowly the animal (dog or cat) will survive, and defibrination of the blood will occur. Similarly the introduction of amniotic fluid into the maternal circulation may render the blood incoagulable. Amniotic fluid infusion is therefore a better term than amniotic embolism and avoids the concept that death is entirely the result of mechanical blockage of the pulmonary circulation by amniotic debris.

Amniotic squames have been demonstrated between the amnion and the chorion, in the placental margin, decidual sinusoids and myometrial veins. They may reach these sites and the maternal circulation by rupture of the membranes in the upper segment of the uterus with eventual escape through the placental site. In low rupture of the membranes the fluid may dissect between the membranes and the wall of the uterus and in rare instances reach the placental margin to enter the venous sinusoids and the systemic circulation, the process being apparently expedited by vigorous uterine contractions. A more frequent outlet however may be through lacerated endocervical veins.

The eventual course of the patient will depend on the concentration of thromboplastin in the amniotic fluid and the rate and amount of auto-infusion. If the amount be large and it be introduced suddenly it will cause sudden death; if more slowly over a long period the blood will become defibrinated with resultant uncontrollable haemorrhage.

The most important predisposing factors influencing the production of the syndrome are tumultuous and exceedingly rapid labour. The use of oxytocic drugs therefore to induce or hasten labour after artificial rupture of the membranes should be condemned. The basic insult in these cases is believed to be intravascular clotting. The extent of this and of consequent defibrination will determine whether the patient will die immediately or will recover temporarily, and if not properly treated will succumb within a few hours from post-partum haemorrhage which is due to afibrinogenaemia, and which will be corrected by the administration of fresh whole blood and fibrinogen. At least 4 g. of fibrinogen should be given but 3 times this amount may sometimes be required before normal haemostasis is restored.

F. J. Browne

271. **Incoagulable Blood in Severe Premature Separation of the Placenta: A Method of Management.**

By A. E. Weiner, D. E. Reid and C. C. Roby. *Amer. J. Obstet. Gynec.*, **66**, 475–499. Sept. 1953. 1 table. 6 figs. 53 refs.

The most common cause of death in abruptio placentae is haemorrhage and shock resulting from it, and the haemorrhage is demonstrated in this article to be associated in many cases with a deficiency in clotting power due to greater or less deficiency of fibrinogen in the blood. The cause of this is not known with certainty but there is much reason to believe that it is due to the passage into the circulation of thromboplastin from the injured uterus. The afibrinogenaemia is not the initial cause of the retroplacental bleeding but its result, and may lead to uncontrollable post-partum haemorrhage following Caesarean section or vaginal delivery. It can be detected by fibrinogen determinations, or by the "clot observation test" which may reveal varying degrees of deficiency. Thus freshly drawn venous blood may fail altogether to clot, or the clot may be small, or it may become fluid within ½ to 1 hour, or when incubated at 37° C it may dissolve within an hour. Such an unstable clot may form when the fibrinogen levels are in the range of the minimal values for haemostasis (100 to 150 mg. per cent) or in the presence of a fibrinolysin, or as a combined effect of both these factors. It signifies that clinically there is ineffective haemostasis and it can be remedied by fibrinogen therapy, 4 to 8 g. usually being necessary.

Ninety to 95 per cent of cases of premature separation of the placenta are of mild or moderate severity. Only 1 or 2 cotyledons may be separated, the foetus is usually alive and clinical signs are of the mildest; shock is absent, but there may be a small area of uterine tenderness. The best treatment is artificial rupture of the membranes followed by Caesarean section if labour does not come on in 2 to 4 hours. In these cases there is no clotting defect and the maternal mortality is negligible. In the severe cases it is necessary at the start of treatment to determine whether or not there is afibrinogenaemia. Blood is drawn from the antecubital vein for the clot observation test which is repeated hourly till delivery. When fibrinogen is decreased to a critical degree initial clotting may be absent. More often clotting occurs followed within an hour by fragmentation and dissolution. The amount of fibrinogen necessary to correct the defect will depend on the clotting behaviour of the blood in subsequent samples. Multiple transfusions are given to combat shock and restore blood volume, the fibrinogen being injected intravenously at the same time. This is followed by artificial rupture of membranes and this by Caesarean section under general anaesthesia if labour has not come on some 4 to 12 hours later. In most cases, however, uterine contractions are good enough to effect vaginal delivery. Post-partum haemorrhage is rare and when it does occur it is due to the clotting defect and the uterus is well contracted. It may be accompanied by haemorrhages elsewhere, including ecchymoses and bleeding from nose and mouth. Hysterectomy is not good treatment in these cases for oozing or active bleeding from pedicles is common after it. Warning is given that Caesarean section should not be done until the clotting defect is remedied, else fatal post-partum haemorrhage may ensue. Other causes of afibrinogenaemia besides severe premature separation are amniotic infusion and long standing intra-uterine death.

F. J. Browne

272. **Maternal Afibrinogenemia Associated with Long Standing Intrauterine Fetal Death.**

By D. E. Reid, A. E. Weiner, C. C. Roby and L. K. Diamond. *Amer. J. Obstet. Gynec.*, **66**, 500–506. Sept. 1953. 4 refs.

This is a record of 6 cases in which the afibrinogenaemia caused uncontrollable post-partum haemorrhage, associated with ecchymoses and bleeding from the respiratory and gastro-intestinal tracts. In certain cases the haemorrhages started before the onset of labour. Hysterectomy, done on 1 patient on account of uncontrollable post-partum bleeding, was followed by oozing from the cervix stump, abdominal wall, etc., and even a finger prick bled so profusely that a pressure dressing was

necessary. In each case the bleeding ceased after intravenous injection of fibrinogen.

The fibrinogen deficiency is supposed to be due to intravascular coagulants derived from autolysis of decidua or placenta and squeezed into the circulation either during Braxton Hicks or labour contractions. No attempt should be made in these cases of intra-uterine death to induce labour as serious haemorrhage may be caused. Expectant treatment should be adopted and the spontaneous onset of labour awaited. Rarely haemorrhagic effects may make termination of pregnancy mandatory. Abdominal delivery is then the best course. Fibrinogen levels must be restored sufficiently to cause stable clot formation at the time of spontaneous labour or before any operation.

[I cannot recall any case like those described in these 3 papers, namely, sudden collapse in labour without obvious cause, or uncontrollable haemorrhage in association with long standing intra-uterine death. But only last week a very competent colleague in a large hospital had a case of post-partum haemorrhage following severe uteroplacental apoplexy. In spite of every method of haemostasis, including massive blood transfusion, bleeding continued and as a last resort hysterectomy was done after which bleeding stopped and the patient recovered. It is evident that fibrinogen is now a necessary item in the obstetric bag.]

F. J. Browne

273. **Pelvic and Femoral Thrombosis in the Female.** By J. STALLWORTHY. *Gynaecologia, Basel*, **138**, 127–134. July 1954. 13 refs.

There has been a progressive decline in deaths from pulmonary embolism in obstetrics and gynaecology in recent years.

The factors predisposing to intravascular clotting include age, heart disease, hypertension, anaemia, local trauma, stasis, sepsis and toxins from degenerating tumours.

Important points in the prevention of thrombosis include early ambulation, encouragement of deep breathing, surgical gentleness, good anaesthesia, good post-operative sedation to encourage early movement and special care in patients suffering from the conditions which predispose to thrombosis.

The method of treatment used by the author consists in an initial dose of 100 mg. (10,000 international units) of heparin injected intravenously. Further treatment is controlled by prothrombin times and the aim is to keep the prothrombin time between 10 and 20 per cent of normal. Tromexan and Dindevan have both been used with success for this purpose.

Paravertebral block or presacral infiltration of the autonomic system are often most dramatic in their effects but the results of anticoagulant treatment are now so good that these procedures are rarely required.

Josephine Barnes

274. **Prevention and Treatment of Thrombosis and Embolism in Gynaecology and Obstetrics by the Use of "Heparin-retard".** (La prophylaxie et le traitement des thromboses et embolies en gynécologie et obstétrique. Emploi de l'héparine-retard.)

By R. BOURG and J. P. PUNDEL. *Gynaecologia, Basel*, **138**, 2–12. July 1954. 30 refs.

Before the introduction of anticoagulants the mortality from pulmonary embolism in the department of obstetrics and gynaecology at the Hospital Brugmann, Brussels, was 0·8 per cent for major operations, corresponding to 30 to 40 per cent of total operative mortality. Anticoagulants have been used since 1949 and there have been no fatal or serious emboli since then. Dicoumarol and Tromexan have been rejected as their action is not always reliable and their effects sometimes dangerous.

Heparin-retard is injected into the anterior surface of the thigh, the initial dose consisting of 35,000 to 50,000 international units of heparin with 3 to 3·5 ml. of polyvinylpyrrolidine, 25 per cent solution (Subtosan) and sometimes 40 mg. of procaine. Careful haemostasis is important and anti-coagulant treatment is controlled by regular observations on coagulation time. The patients are mobilized early and the legs are bandaged with elastic adhesive tape. In puerperal cases, prophylaxis is confined to those patients where there appears to be special risk of thrombosis and embolism.

The results have been encouraging since in about 2,000 gynaecological operations there has been no fatal case of embolism. In 111 cases treated for post-operative puerperal or medical thrombosis only 1 developed embolism and this was not fatal.

Josephine Barnes

275. **Haemorrhages due to Afibrinogenaemia in Obstetrics.** (Les hémorragies par afibrinémie en obstétrique.)

By P. GUILHEM, A. PONTONNIER, R. BAUX, M. MONROZIES and R. BLANC. *Gynéc. Obstét.*, **53**, 219–232. 1954 (Bibliography given in Thesis by R. Blanc, University of Toulouse, 1953.)

Three theories concerning the aetiology of the condition in which the fibrinogen in the blood disappears are discussed.

These comprise, firstly, the fibrinolysis theory where it is thought an abnormal protease is circulating in the blood.

Secondly, the thromboplastic theory where the fibrinogen is believed to be transformed into fibrin even within the blood vessels.

Thirdly, cessation of the synthesis of fibrinogen within the liver and thence its disappearance in the circulation.

The authors report 8 cases of severe bleeding associated with afibrinogenaemia. The symptoms, aetiology, pathology, and treatment, are all described. They defend the thromboplastic theory which to them seems to fit the clinical facts and biological findings. They also show that minor forms of this complaint exist which are much more common than is usually thought. Finally they advise certain principles of treatment, the chief of which is the intravenous infusion of plasma, and in grave cases the performance of Porro's operation.

D. Maxwell

276. **Comparative Studies of Coagulation Factors in Maternal and Foetal Blood obtained during Umbilical Cord Pulsation.** (Vergleichende Untersuchungen der Blutgerinnung im mütterlichen und kindlichen Blut bei noch pulsierender Nabelschnur.)

By H. RUNGE, I. HARTERT and W. EICHER. *Gynaecologia, Basel*, **138**, 337–349. Aug. 1954. 6 figs. 44 refs.

In 20 cases simultaneous studies of various blood coagulation factors were carried out in blood obtained from the mother and from the still-pulsating umbilical cord. Separate samples were studied in a larger number of cases.

The following results were obtained. Coagulation time is decreased in both mother and newborn child. The decrease is most pronounced in the child, where it reaches very low levels. The prothrombin index varies in the mother at about the upper limit of normal, and in the child at about the lower limit of normal. It is always lower in the child than in the mother. Thromboelasticity is increased in both mother and child, but is more increased in the mother. The number of platelets is normal or decreased in the mother and usually decreased in the child. The difference is not great. Maternal blood fibrinogen is nearly always greatly increased. The fibrinogen content of the umbilical cord blood is greatly decreased, often to a fraction of the maternal level. Fibrinolysis was never observed in maternal blood but it was found in the umbilical cord blood in 5 out of 20 cases.

Josephine Barnes

277. **Incoagulability of Blood after Accidental Haemorrhage.**

By H. C. MOORE. *Brit. med. J.*, **2**, 277–279. July 31, 1954. 10 refs.

The author, Director of Pathology, the Rotunda Hospital, Dublin, describes a case of severe post-partum haemorrhage following accidental haemorrhage. The patient, a 10-para was admitted with a history of vaginal bleeding at the 30th week of pregnancy. Following an eclamptic fit, she was delivered of a stillborn foetus by forceps. The placenta followed at once, with a large retroplacental clot. In spite of ergometrine, and packing the uterus, post-partum haemorrhage continued uncontrolled. The blood was watery, and did not clot. Massive blood transfusion, including fresh blood, did not control bleeding or shock. Finally 2 g. of fibrinogen was given intravenously, and within 15 minutes all bleeding ceased. Within 25 minutes the clotting time was 4 minutes.

The author reviews the literature and discusses possible causes for this disturbance in the mechanism of coagulation. It evidently follows accidental haemorrhage rather than precedes it, for the retroplacental blood is clotted. There is a reduction in fibrinogen, with a fall in blood prothrombin, and a fibrinolysin is present. Some evidence supports the view that the body fibrinogen is used up in the formation of multiple small thrombi in many organs, following leakage of thromboplastin from the placenta.

Although this particular complication of accidental haemorrhage is probably not common, the author stresses that blood transfusion is not successful in treatment, and a supply of fibrinogen should be available to all obstetric hospitals.

Eileen Wilson

278. **The Pathogenesis, Diagnosis and Prevention of the Post-thrombotic Syndrome.** (Zur Pathogenese, Diagnostik und Prophylaxe des postthrombotischen Syndroms.)

By T. HALSE. *Gynaecologia, Basel*, **138**, 32–48. July 1954. 7 figs. 1 ref.

The post-thrombotic syndrome can be studied by phlebography of the veins of the lower extremities. In the post-thrombotic syndrome, valvular incompetence is frequently found. This can be improved by resection of the femoral vein. This operation was undertaken in 78 cases out of a total of 232 studied with permanent improvement in 71 per cent. The favourable result is indicated in the results of phlebographic studies before and after operation.

Prevention and prompt treatment of thrombosis may prevent the development of the post-thrombotic syndrome. In a series of cases where dicoumarol was used for prophylaxis or treatment of thrombosis, the eventual incidence of post-thrombotic symptoms and signs was much better than in a comparable series of cases not so treated.

Josephine Barnes

279. **Prophylactic Hormone Therapy.**

By G. V. SMITH and O. W. SMITH. *Obstet. Gynec.*, **4**, 129–141. Aug. 1954. 6 tables, 34 refs.

From the prolific and always stimulating pen of these Boston research workers comes another article on the value of stilboestrol therapy in certain complications of pregnancy. Their well-known view that abortion, premature delivery, toxaemia and intra-uterine death are associated with a decreased placental secretion of oestrogen and progesterone is further substantiated in this article. Pregnanediol excretion in 104 women who developed one of these complications dropped or failed to rise during a 3½- to 8-week interval before trouble manifested itself clinically. These authors claim that oxidation products of oestrogen are necessary for placental secretion of progesterone. Elevated urinary pregnanediol excretion follows stilboestrol administration and lowered levels follow its withdrawal, but stilboestrol therapy does not always stimulate placental luteal function. The Smiths state that overdosage with stilboestrol in the early weeks of pregnancy and the erratic taking of this drug at any time may actually precipitate trouble in women with borderline placental function. However they produce further proof of its clinical efficacy in properly regulated dosage in 81 cases of habitual abortion, 61 premature babies, 42 diabetics and in toxaemia.

J. G. Dumoulin

280. **Hyperemesis Gravidarum Treated by Feigned Interruption of Pregnancy.** (Su due casi di iperemesi gravidica trattati con interruzione simulatadi gravidanza.)

By G. GIOCOLI. *Minerva ginec., Torino*, **6**, 105–106. Aug. 31, 1954.

Discussing two cases of incoercible hyperemesis successfully treated by feigning to terminate the pregnancy, the author points out that such a line of treatment can be but rarely justified. Although it may actually succeed, it is likely fatally to undermine the patient's confidence in her medical attendant and in the medical profession generally. It may do irreparable harm to an already unstable psyche; at best it will force an attitude of discontented resignation and resentment.

W. C. Spackman

281. **Indications for and the Scope of Indirect Placentography in the Diagnosis of Placenta Praevia.**

By U. BORELL, I. FERNSTRÖM and A. WESTMAN. *Acta obstet. gynec. scand.*, **33**, 231–252. 1954. 7 figs. 40 refs.

This is a review of the hospital records and the radiographs of 192 women who attended the Karolinska Hospital, Stockholm, between 1940 and 1953, because of painless vaginal bleeding during the last trimester of pregnancy, and were examined by indirect placentography after instillation of a contrast medium into the bladder and of air into the rectum.

In 155 out of the 192 cases the results of indirect placentography were in agreement with clinical localization (ascertained at Caesarean section, by internal examination, or by inspection of the placenta) and in 26 cases the results of clinical and radiological examination differed; there were 10 false positive and 16 false negative radiological diagnoses of placenta praevia. Eleven times it was not possible to interpret the radiological appearances because the presenting part was not sufficiently low; in 5 of these cases there was transverse lie, in 4 a breech presentation, and twice the patients were examined during the seventh and eighth lunar month respectively and the presenting head was too high. In such cases it appears reasonable to use direct placentography (soft tissue radiography) or arteriography.

[The original paper must be consulted for technical details.]

N. Alders

282. **Toxemia of Pregnancy and Post-Toxemic Hypertension.**

By L. C. CHESLEY. *Gynaecologia, Basel*, **138**, 259–275. Aug. 1954. 7 figs. 42 refs.

Data obtained from repeated re-examination of women who have had eclampsia are discussed in the light of the available literature on post-toxaemic hypertension.

The clinical studies have revealed that the incidence of hypertension is significantly increased in women who have suffered from toxaemia of pregnancy compared with an unselected group of women. Post-toxaemic hypertension is nearly twice as common after pre-eclampsia as after eclampsia.

It is concluded that the nature of post-toxaemic hypertension is so far not settled. There is no definite anatomical basis in the form of vascular or renal damage. There is a definite correlation between the duration of toxaemia and the subsequent incidence of hypertension. The author concludes however that this method of approach does not answer the question of the relationship between toxaemia of pregnancy and post-toxaemic hypertension.

[This is a thoughtful review by an author whose views on the important subject of the sequelae of toxaemia of pregnancy have been known for many years.]

Josephine Barnes

283. **Investigation on the Role of Adreno-cortical Hormones in the Pathogenesis of Eclampsia.** (Z badan nad rola hormonow kory nadnerczy w patogenezie rzucawki.)

By T. ZIELINSKI. *Ginek. polska.*, **25**, 207–219. Apr.–June 1954. 33 refs.

Taking as a basis the findings described in the literature about the role played by the cortical steroid hormones in the pathogenesis of pre-eclamptic toxaemia and eclampsia the author undertook to determine the activity of the adrenal cortex in these states by quantitative estimation of the excretion of 17-ketosteroids.

In 16 cases of pre-eclamptic toxaemia and 9 cases of eclampsia he found the amount of 17-ketosteroids in the urine to be normal or slightly decreased. The amount observed in eclampsia is as a rule decreased. From this the author concludes that in pre-eclamptic toxaemia and eclampsia there is no increase in the activity of the adrenal cortex.

The comparison of this observation with those of other authors, who found a large increase in the excretion of cortico-steroids in pre-eclamptic toxaemia and eclampsia, gives the idea that in advanced pregnancy there exist other sources of bodies of cortico-steroid character besides the mother's adrenal cortex. After reviewing the arguments pointing to the extra-adrenal production of cortico-steroids, the author comes to the conclusion that the placenta is the source of the increased amount of cortico-steroids in eclampsia.

S. H. Riterband

284. **Mechanism of Sodium Retention in Pre-eclamptic Toxemia.**

By E. S. GORDON, J. J. CHART, D. HAGEDORN and E. G. SHIPLEY. *Obstet. Gynec.*, **4**, 39–50. July 1954. 6 figs. 5 tables. 26 refs.

Using a method which depends upon the sodium excretion of adrenalectomized male rats maintained under standard conditions of salt loading, injected with a urinary extract from pregnant women, the authors claim that the urine of cases of pre-eclamptic toxaemia contains a sodium-retaining factor (SRF). The production of SRF is at a low level in normal pregnancies, and only slightly elevated in some cases above that seen in normal men and non-pregnant women. In toxaemic patients, the excretion level is invariably elevated. The elevated level fluctuates within wide limits and disappears following termination of pregnancy. In placental extracts from toxaemic cases there is no appreciable SRF. The adrenal gland is possibly associated with the production of SRF, although there is, as yet, little proof of this. Another factor in its appearance in excessive amounts may be

impairment of liver function. SRF is presumed to function through a renal tubular mechanism.

J. G. Dumoulin

285. **Haemostatic Defects and Increased Red Cell Destruction in Pre-eclampsia and Eclampsia.**

By J. A. PRITCHARD, O. D. RATNOFF and R. WEISMAN. *Obstet. Gynec.*, **4**, 159–164. Aug. 1954. 17 refs.

Haematological defects have been found by the authors who studied 13 cases of pre-eclampsia and 9 eclamptics. The most common clotting defect was a prolonged thrombin time which was obtained in 19 of the 22 cases and which varied with the severity of the toxaemia. Six eclamptics and 1 pre-eclamptic had a significant thrombocytopenia, but only 3 cases had prolonged bleeding times and they also showed an increase in capillary fragility. Several patients in whom thrombocytopenia was not demonstrated gave a history of nose bleeds, bleeding from the gums or skin petechiae, and all the cases with definite thrombocytopenia had noted these abnormalities. Haemoglobinaemia and haemoglobinuria was present in 3 eclamptics. Increased red blood cell destruction was suspected in several other patients. The authors were unable to detect agglutinins or haemolysins in the maternal blood or antibodies active against maternal erythrocytes in the infants' plasma. The pathogenesis of these haematological abnormalities is not known. *J. G. Dumoulin*

286. **Remote Deaths Following Eclampsia.**

By L. C. CHESLEY and R. A. COSGROVE. *Obstet. Gynec.*, **4**, 165–176. Aug. 1954. 8 tables. 9 refs.

Twenty-seven women died in eclampsia in 296 cases of this condition occurring between 1931 and 1951 at the Margaret Hague Hospital, New Jersey. Two hundred and sixty-two of those cases leaving hospital were followed up from 1 to 21 years. Nineteen (7·2 per cent) had died, 11 from cardiovascular–renal disease. In those who had eclampsia in their first pregnancy the remote mortality was 4·5 per cent, whilst in the multiparous it was 15·6 per cent. The authors proceed to compare the expected death rates with the observed death rates in their cases, dividing them according to parity and race (white and negro). They find that the remote annual death rate in post-eclamptics is double that for unselected women of the same ages and races. White women having eclampsia in their first pregnancy do not show any increase in the remote annual death rate. White multiparas who have eclampsia have a considerably increased remote mortality. This probably depends upon a high incidence of antecedent hypertensive disease. Negro women show a markedly increased remote mortality. Recurrent toxaemia of pregnancy is also associated with an increase in the remote annual death rate. *J. G. Dumoulin*

287. **Pregnancy Following Malignancy.**

By W. B. THOMPSON. *Amer. J. Obstet. Gynec.*, **67**, 810–821. Apr. 1954. 13 figs. 4 refs.

This is a report on 10 women who became pregnant after operations for malignant disease, 8 of them for cancer (breast, ovary, skin and bowel) and 2 for sarcoma of bone. There was no evidence that pregnancy favoured recurrence and this did not take place in any of the cases. The author concludes that child-bearing may not be impossible after malignant disease has been detected and obliterated. When there seems to be a reasonable certainty that the malignancy has been conquered the patient may be assured that she is not undertaking any additional risk. The high oestrogen levels of pregnancy did not seem to have any carcinogenic effect.

F. J. Browne

288. **Pregnancy with Diabetes—the Physician's Viewpoint.**

By F. H. H. WILSON. *Med. J. Aust.*, **2**, 87–88. July 17, 1954. 4 refs.

Diabetes does not usually prevent a woman from having children but special care is needed in pregnancy. There is some chance of the baby developing diabetes in later life, but it is not great unless the father is diabetic or has a diabetic parent. With efficient obstetrical and medical care, there is very little added risk to the mother, and very rarely is the condition worse after pregnancy. However, diabetic vascular degeneration may increase during pregnancy so that in severe diabetic retinopathy the remaining vision may be endangered. Pregnancy in the diabetic is associated with an increased incidence of congenital defect and of pre-eclampsia and an increased liability to death *in utero* or in the first few days of life.

The infant tends to be oversized, though needing the same care as any premature child and liable to die during labour. Foetal risks are greater in the presence of maternal vascular complications of diabetes especially nephropathy or calcification of the pelvic arteries.

Insulin requirements during pregnancy show a gradually increasing need which in such cases may reach 4 times the original dose. After delivery it falls at once to the original level.

To avoid diabetic acidosis infection must be promptly treated. During labour the exertion and the reduced food intake mean that much less insulin will be required. So it is best to test the urine every 4 hours during labour and give ordinary insulin according to the results of the urine tests.

During lactation calories must be adjusted to maintain the mother's weight and reduced after weaning to prevent obesity.

Routine care of all infants of diabetic mothers includes postural drainage, aspiration of the upper air passages and stomach, administration of oxygen and chemotherapy and dehydration for 48 hours.

S. Devenish Meares

289. **The Obstetrician's Viewpoint of Diabetes in Pregnancy.**

By R. O. GILL. *Med. J. Aust.*, **2**, 88–89. July 17, 1954. 8 refs.

The author reviews some of the literature and concludes that the maternal mortality in diabetic mothers is 30 times that in healthy mothers.

During the last 3 months of gestation the foetus is in

constant danger. The risks are death *in utero* due to toxaemia or some complication of the diabetic state, prematurity, death during labour, or neonatal death. (Hydramnios may precipitate premature labour.)

Pregnancy should be terminated before term as a routine, preferably by Caesarean section.

The foetal survival rates recently reported in the literature vary from 54 to 78·5 per cent.

S. Devenish Meares

290. **Pregnancy with Diabetes. Discussion of the Papers by F. H. H. Wilson and R. C. Gill.**

Med. J. Aust., **2**, 110–113. July 17, 1954.

D. R. Sheumack gave the figures from the Royal Hospital for Women. There were 69 cases of diabetes amongst 56,500 women who had been confined since 1935. There was 1 maternal death, The overall foetal survival rate was 69·5 per cent. Up to 1948 the overall foetal survival rate was 66 per cent; since that time it had been 75 per cent. Toxaemia occurred in 44·9 per cent. The majority of the babies weighed about 7 pounds; only 10·1 per cent weighed over 10 pounds. In most cases pregnancy should be terminated at the 37th week. For primiparae and for severely diabetic multiparae a lower segment Caesarean section under general anaesthesia was the method of choice.

David McGrath gave the figures from the Women's Hospital, Crown Street. For the period 1944 to 1953 there were 66 diabetic patients with 72 pregnancies, an incidence of roughly 1 in 600. Toxaemia had occurred in 61 per cent. The total foetal wastage was 19·4 per cent and the maternal death rate was 1·3 per cent. Caesarean section was performed in 8·3 per cent of cases. The following circumstances would influence one towards induction of labour: difficulty in the control of the diabetes, very rapid growth of the foetus, toxaemia and hydramnios.

S. Devenish Meares

291. **Thoracoplasty in Women with Twin Pregnancy.** (Torakoplastyka u kobiety z ciaza bliźniacza.)

By W. Rzepecki and B. Bogucki. *Ginek. polska.*, **25**, 185–190. Apr.–June 1954. 3 figs. 9 refs.

The author gives a preliminary report on a case of twin pregnancy complicated by pulmonary tuberculosis. A two-phase thoracoplasty was performed at 5 months gestation. The pregnancy resulted in a full-time normal delivery. Three months later the mother and infants were doing well.

He mentions 11 other cases of pregnant mothers treated by thoracoplasty or by extrapleural pneumothorax with no harm to the pregnancy and subsequent delivery. The author points out the view generally accepted: treat the disease and leave the pregnancy alone.

S. H. Riterband

292. **Rheumatic Heart-Disease in Pregnancy.**

By M. MacLeod. *Lancet*, **2**, 668–671. Oct. 2, 1954. 2 tables. 20 refs.

This paper is based on the consideration of 100 cases of rheumatic heart disease in pregnancy. There were no maternal deaths in the series of 83 cases of mitral stenosis and 17 of mitral stenosis plus aortic incompetence. The author points out that there are two main circulatory effects of mitral stenosis, viz., pulmonary hypertension and right ventricular failure leading to congestive failure which tends to occur in the older patient. Pulmonary hypertension, leading to orthopnoea, increasing dyspnoea, cough with frothy sputum, haemoptysis and finally pulmonary oedema, is responsible for most of the symptoms in pregnancy. The effect of pregnancy with its increased total blood volume and cardiac output is to accentuate the natural features of mitral stenosis. Evidence of severe disability either during a previous pregnancy or in the period preceding the pregnancy under review is an important factor in assessing the risk. Rapid heart rates, as with auricular fibrillation, impair diastolic filling of the left ventricle and raise the pulmonary pressure. Any condition which increases the venous return to the heart and the cardiac output, such as emotional disturbances or infection with fever, will also increase the pulmonary hypertension and hence may result in acute pulmonary oedema in these patients. In the management of these patients physical rest, sedation, and reassurance are very important. Anaemia must be dealt with, any infection treated thoroughly with bed rest and penicillin given during the puerperium to prevent bacterial endocarditis. Labour by vias naturales is the method of choice with operative interference in the form of forceps or Caesarean section as dictated by obstetrical considerations. Spinal anaesthesia, since it reduces the venous return to the heart, is advocated for any operative interference. Twelve of the patients in the series had a therapeutic abortion carried out during the early months of pregnancy because of severe pulmonary symptoms or congestive failure early in pregnancy. The author concludes that early recognition and treatment of pulmonary hypertension will contribute to a reduction of the maternal mortality.

H. H. Fouracre Barns

293. **Poliomyelitis with Pregnancy.**

By J. S. Hunter and C. H. Millikan. *Obstet. Gynec.*, **4**, 147–154. Aug. 1954. 23 refs.

This is a study of 49 patients at the Mayo Clinic who had pregnancy complicated by acute anterior poliomyelitis. The maternal mortality was 6 per cent and the foetal loss 32 per cent. The authors show that there is an increased susceptibility to this disease in pregnant women, but not an increased mortality from it. The bulbar spinal type of disease was present in 22 per cent of the cases. No one trimester of pregnancy is associated with a more severe type of poliomyelitis. The disease need not alter the obstetric management of the case. The incidence of miscarriage may be increased as a result of poliomyelitis. The disease can occur in the infant in the immediate neonatal period.

J. G. Dumoulin

294. **Advanced Extrauterine Pregnancy.**

By G. King. *Amer. J. Obstet. Gynec.*, **67**, 712–740. Apr. 1954. 6 figs. 6 tables.

In this Joseph Price Oration for 1953 the author, after reviewing the history of the subject, describes 12 cases of

advanced extra-uterine pregnancy in his own clinic. Duration of the pregnancy varied from 38 weeks to over 20 years, but in only 1 case were the foetal heart sounds audible when the patient came under treatment, and this baby survived. In 3 others the foetus had died recently. A history of false labour, usually at term, but once at 47 weeks, was obtained in 6 patients, in 5 of whom a uterine cast was passed. Braxton Hicks contractions are absent, and the lie of the foetus is often abnormal, but a radiological examination is the most useful diagnostic aid. A plain film may demonstrate a foetus in an abnormal position or attitude, or show an abnormally thin soft tissue covering, instead of a uterine shadow of normal thickness. Failure of the foetus to change position is also suggestive. The absolute diagnosis depends on hysterosalpingography and the demonstration of foetal parts lying outside the uterus.

The best treatment is laparotomy as soon as diagnosis is made, the only possible exception being if the foetus is near viability, when a wait of 2 or 3 weeks may be permissible. If possible the placenta should be removed, but if this carries too great a risk it may be left and the abdomen closed. This was done in 1 case and the patient never had any troublesome after-effects, but it took 3½ years before the placenta ceased to be palpable on bimanual examination. There was 1 living child at term, without deformity, and now, aged 7 years, she is in every sense a normal and intelligent girl.

[This is a valuable paper worthy of careful study, especially as it contains an excellent historical survey and an account of operative details, difficulties and dangers.]

F. J. Browne

295. **Tubal Pregnancy and Endometriosis.** (Gravidanza tubarica ed endometriosi.)

By F. Ferraris. *Minerva ginec., Torino.*, **6**, 561–564. Aug. 15, 1954. 29 refs.

One of the theories put forward to explain extra-uterine implantation of the ovum is that which requires that there shall be ectopic fragments of endometrium growing at the site of implantation to attract the ovum, such as might be found in cases of pelvic endometriosis. The author made careful serial sections of pregnant tubes from 15 cases but failed to find any trace of endometrial tissue in any of them. He therefore considers that this theory is without basis.

W. C. Spackman

LABOUR

296. **Support During Labour.**

By H. Thomas and E. Wiedenbach. *J. Amer. med. Ass.*, **156**, 3–5. Sept. 4, 1954. 2 refs.

The change from obstetric care in the home to that in hospital has brought untold benefits in safety for mother and child, but from the psychological point of view the actual management of labour in some hospitals leaves much to be desired. Particular mention is made of the central nursery system, the exclusion of husbands during the labour period, the use of a general first stage room, and the use of heavy sedation to obliterate the mother's memory of childbirth.

Support during labour depends for its effectiveness not only on the sympathy and interest of those in attendance but on their comprehensive understanding of the physical and psychological aspects of the birth process and the preparation of the mother beforehand. Training for Childbirth is strongly advocated by the authors and an outline is given of the "Support Program" followed during labour at the Department of Obstetrics, Yale University. This includes relaxation, frequent attention in a private room, a reasonable amount of information of the progress of labour, the presence of the husband when possible in the first stage, anaesthetic agents if desired, and a cheerful encouragement at all times.

Before discharge from hospital 142 cases received a questionnaire in order to obtain some evaluation of the mother's own assessment of her labour. One of these is reproduced in full with the patient's answers, and an analysis of the series was found to be helpful in improving the methods used.

[There is much food for thought in this paper on a much neglected aspect of hospital delivery.]

D. W. James

297. **A Study of 51 Recordings of Uterine Contractions in the Course of Labour by the Electronic Tokodynamometer According to the Method of Reynolds.** (Étude de 51 enrigistrements de contractions utérines au cours de travail par la tokodynamométrie électronique (méthode de Reynolds).)

By M. Mayer, C. Kazancigil, C. Bugnard and A. Sahy. *Gynéc. Obstét.*, **53**, 188–218, 1954. 11 figs. 26 refs.

The electric dynamanometer of Reynolds improves the possibilities of studying the function of the uterus in labour.

One isolated reading of the tocodynamometer tracing cannot lead the observer to conclusions either as regards the physiology or the pathology of the uterus.

Correct interpretations on tracings are based on the following conditions:

1. The technique of obtaining the tracing must be impeccable.
2. The tracings must not be limited to a very short period of labour, but continued through successive periods of 20 minutes, covering if possible the entire duration of the confinement.
3. The interpretation of the curves must take into account the clinical and physiological circumstances under which the instrument was used.

Three groups of cases were chosen to make up a total of 51 recordings:

(1) Precipitate labours brought about by various oxytocic drugs.
(2) Trial labours using 3 types of drugs.
  (*a*) Antispasmodics.
  (*b*) Antihistamines.
  (*c*) Ganglioplegics.
(3) Normal labours—under this group were included

painless labours or patients adequately prepared by relaxation methods.

The writers came to 5 conclusions:

(1) They confirm the findings of Reynolds and his colleagues as far as oxytocic drugs go (pitocin in particular) and they stress the great advantages of using this series by intravenous infusion.

(2) The comparison of the effects of the oxytocic drugs with the synthetic series such as methergine showed that the latter are effective and that the level of their action is low and less subject to the individual idiosyncrasy frequently seen with the oxytocic group.

(3) This instrument confirms the finding that the most active area of the uterus is the fundus. The persistence or appearance of true contractions in the lower segment corresponds to a functional state which is only seen: (*a*) in patients experiencing apparent painful sensations which do not correspond to true labour; (*b*) in patients in true labour which is complicated by abnormal types of contractions.

(4) The analysis of curves is only of value if they are recorded from all 3 sites on the uterus simultaneously —namely, at the level of the fundus, middle third, and lower segment.

(5) Abnormal clinical findings in labour can often be predicted by careful perusal of tracings.

D. Maxwell

298. **The Normal and Abnormal Contractile Waves of the Uterus During Labour.**

By H. ALVAREZ and R. CALDEYRO-BARCIA. *Gynaecologia, Basel*, **138**, 190–212. Aug. 1954. 16 figs. 20 refs.

The authors describe the results they have obtained by studying the contractile waves of the uterus during labour. Studies have been carried out by measurement of intra-amniotic pressure and also by electro-manometric recordings of the uterine activity in different areas of the uterus.

As a result 5 different types of uterine activity have been demonstrated:

1. Normal wave with total coordination. This starts in a pace maker at the fundus and is stronger and of a greater duration in the upper segment than in the lower. Efficient dilatation of the cervix accompanies this.

2. Contractions which are stronger in the lower than in the upper segment. These are associated with a tendency to slow labour.

3. Two types of ascending waves, that is from the lower to the upper segment. These are associated with a slow dilatation of the cervix.

4. First degree incoordination. Here the uterus shows two separate zones of functional activity which operate independently of one another. The progress of labour is slow.

5. Second degree incoordination or uterine fibrillation. Here the uterus is divided into several independently contracting zones and labour does not progress at all. There is high tonus in the uterus itself and small irregular contractions of high frequency.

Spontaneous changes in the type of uterine activity may occur during the actual course of labour.

[The valuable work of these authors in the study of uterine activity during labour is already well known in this country. This is an abstract of their paper to the International Congress of Obstetrics and Gynaecology at Geneva in July, 1954. The same authors presented similar work in the *Journal of Obstetrics and Gynaecology of the British Empire*, 1952, **59**, 646.]

Josephine Barnes

299. **Hazards of Surgical Induction of Labour.**

By G. EVANS. *Lancet*, **2**, 564–567. Sept. 18, 1954. 10 tables. 10 refs.

The author records the results of surgical induction of labour in 843 patients between the years 1928–1952. The incidence of induction was 3·3 per cent (843 in 25,960 pregnancies). The methods of surgical induction used were insertion of stomach tube, animal bladder, Krause bougie or amniotomy, the last method being used almost exclusively since 1945. General anaesthesia was administered in all cases of induction but prophylactic chemotherapy was not used. The maternal mortality was 7 in 843 cases of which 3 deaths were considered attributable to the induction itself. In one a marginal placenta praevia was separated with a Drewe-Smythe catheter producing haemorrhage and shock; in the second the mother died of puerperal sepsis associated with paralytic ileus and terminal perforation of the caecum following a forceps delivery; and in the third case the mother died of puerperal sepsis due to *Pseudomonas pyocyanea*. Using the old standard of notifiable puerperal pyrexia there were 91 (10·8 per cent) morbid mothers. It was found that the incidence of genital sepsis and urinary infection was about three times as great as in non-induced labours. The method of induction used did not influence significantly the mortality rate as a whole or the incidence of genital infection, but the longer the induction-delivery interval the greater the morbidity. There were 102 stillbirths and 33 neonatal deaths making a total foetal loss of 135 (15·6 per cent). Of these there were 16 stillbirths and 1 neonatal death considered attributable to the induction of labour, giving a total foetal mortality of 2·02 per cent. Two deaths were due to separation of the placenta with a stomach tube, 3 were due to intra-partum infection resulting from the induction, 11 were due to prolapse of the cord and the neonatal death was due to *Bacterium coli* meningitis. Prolapse of the cord was approximately 2½ times more common when the foetal head was not engaged at the time of induction than when it was engaged. In 25,117 non-induced labours there were only 2 stillbirths due to intra-partum infection and 30 to prolapse of the cord. The author suggests that, when surgical induction is indicated and the head is engaged, rupture of the forewaters should be employed. When the head is not engaged the hazards are greater and, unless the condition for which the operation is being considered carries a foetal mortality of more than 2 per cent, surgical induction should be avoided. The author concludes that the greatest single factor influencing the onset of complications after surgical induction is the position of the head at the time of induction. If the head is not engaged

there is a higher maternal mortality due to prolongation of the induction-delivery interval and an increased foetal loss due to higher incidence of prolapse of the cord.

H. H. Fouracre Barns

300. **Compound Presentation of Brow, Foot and Hand at Term. A Case Report.**

By H. E. Bowles. *West. J. Surg. Obstet. Gynec.*, **62**, 428–430. Aug. 1954. 1 fig. 5 refs.

The author, from the Kipiolani Maternity Hospital, Honolulu, reviews the aetiology and treatment of compound presentations. The predisposing factors are multiparity, poor tone of the recti and contraction of the pelvic inlet. Diagnosis may be made by vaginal examination or radiology and treatment depends on the limbs presenting. The commonest type with a hand down beside the head seldom causes serious difficulty as the hand can usually be replaced while obstetric forceps are applied or an internal version with breech extraction performed. When deep pelvic impaction has occurred or where there is little amniotic fluid left in the uterus, Caesarean section is the method of choice.

The author's case occurred in a 29-year-old patient with 2 previous normal deliveries. She was obese and had a flabby abdominal wall but her pelvic measurements were not recorded although the pelvis is described as roomy. She went into labour at term and when the cervix was 5 cm. dilated the right hand and left foot were found to be prolapsed beside a low presentation. No progress was made for 24 hours and attempts to correct the malpresentation failed. A lower segment Caesarean section was performed with slight difficulty and a living child delivered. The mother made an uneventful recovery.

D. C. A. Bevis

301. **Vulvar Condylomata Acuminata Complicating Labour.**

By R. L. Gorthy and M. A. Krembs. *Obstet. Gynec.*, **4**, 67–74. July 1954. 29 refs.

Condylomata acuminata undergo pronounced hypertrophy during pregnancy. They may extensively involve the vulval region, perineum and vagina, and their growth may be stimulated by the increased vaginal secretions associated with pregnancy. Although referred to as venereal warts, gonorrhoea and syphilis do not seem to be aetiological factors. Successful treatment has been reported using radium (75 to 450 mg. hr.), podophyllin (25 per cent in mineral oil), colchicine in oil, immunotherapy, electrocoagulation, Fowler's solution (an arsenical), antibiotics, surgical excision, and other therapeutic measures, which suggests that no one treatment is universally adequate. The authors believe that antibiotics are essential in the majority of cases because of the high incidence of secondary infection. Many condylomata regress spontaneously so that treatment with antibiotics will suffice in many lesions associated with pregnancy. Podophyllin has been used successfully in pregnancy, but it does not always cure, and the authors believe that its absorption may cause toxic effects to mother and foetus. Delivery by Caesarean section is occasionally indicated in very severe lesions.

J. G. Dumoulin

302. **Intramuscular Ergometrine and Hyaluronidase in Prevention of Post-partum Haemorrhage.**

By N. Kimbell. *Brit. med. J.*, **2**, 130–131. July 17, 1954. 2 refs.

An assessment is made of the effect of adding 1 mg. of hyaluronidase to intramuscular injections of ergometrine given prophylactically at the time of crowning or delivery of the head. All cases reviewed were women delivered by midwives in the left lateral position. A control series of 747 deliveries in 1950 before prophylactic ergometrine was used showed a post-partum haemorrhage rate of 6·4 per cent, with manual removal of the placenta in 1·6 per cent of cases. Ergometrine 0·5 mg. was used alone in 198 cases with a post-partum haemorrhage rate of 3·5 per cent and 0·5 per cent of manual removals. Results were comparable to this when hyaluronidase was added to 0·25 mg. ergometrine, but, when the larger dose of ergometrine was used with hyaluronidase in 1,728 cases, only 0·9 per cent of cases had a loss of 20 ounces or more. In this last group, the manual removal rate was 1·1 per cent. The length of the third stage of labour was so reduced that in the ergometrine and hyaluronidase group it was completed in under 10 minutes in 51 per cent of cases, compared with 22 per cent in the control group.

Timing is most important and placental expression should be carried out as soon as possible.

A plea is made for the adoption by midwives of the technique of giving ergometrine and hyaluronidase at the time of crowning of the head.

Doreen Daley

303. **A Fatal Case of Post-partum Haemorrhage due to Fibrinolysin.** (Su di un caso di sindrome emorragica fibrinolitica post-partum.)

By F. Marchesi. *Minerva ginec., Torino*, **6**, 445–447. June 15, 1954. 15 refs.

A case is described and discussed of a fatal post-partum haemorrhage due to failure of effective clotting of the blood. The patient, a primipara 8-months pregnant, had shown a tendency to bleed from the gums and to suffer from epistaxis. She was delivered normally in her own home but removed to hospital for a post-partum haemorrhage uncontrolled by ordinary means including gauze packing of uterus and vagina. She continued to have severe unceasing oozing and died soon after in spite of a moderate blood transfusion whilst other measures were being prepared. Blood flowing from the vagina coagulated in a few minutes but the clot redissolved completely in 15 minutes and remained liquid thereafter. There was no failure of uterine contraction.

It is suggested that there is in such cases either a fibrinogenopenia due to the blood fibrinogen having been used up (e.g., by a preceding accidental haemorrhage) or that a fibrinolysin is present temporarily in excess which dissolves any clot almost as soon as it is formed.

[This condition is now well known and a similar (non-fatal) case has recently been described and discussed (see Abstract 277) where tests designed by Schneider and Weiner are given and it is urged that all obstetrical hospitals should carry a supply of fibrinogen to meet the emergency. This case was successfully treated with 2 grammes of fibrinogen intravenously.]

W. C. Spackman

ANAESTHESIA

304. Modern Changes in the Attitude Towards the Pain of Labour.

By G. J. HALL. *Med. J. Aust.*, **2**, 289–291. Aug. 21, 1954.

There is pain in normal labour and the author always tells this fact to his patients. Antenatal education relieves the fears of labour. Antenatal exercises assist training in relaxation. The amount of pain varies with the degree of relaxation. Obstetricians do not spend sufficient time in the labour ward.

Pethidine in the late first stage assists relaxation and hastens dilatation of the cervix. Hyoscine is used in the late first stage only and if its administration is carefully controlled then the patient can be made to "come out" of the hyoscine in the second stage.

The author prefers nitrous oxide and oxygen for the second stage, relegating trilene to use by country practitioners.

Delivery of the head over the perineum is painless if relaxation is satisfactory. Perineal anaesthesia as the head is crowned is greater in primiparae than multiparae. Hall has found that sacral massage and the presence of a close confidant will do more to relieve pain than all drugs. Noise may indicate hard work rather than pain.

S. Devenish Meares

305. Evaluation of Nisentil as an Analgesic Agent in Labour.

By H. J. HUGHES and N. W. PHILPOTT. *Canad. med. Ass. J.*, **71**, 6–8. July 1954. 6 tables. 6 refs.

A report is given of the response to Nisentil administered during labour to 100 patients delivered in the Royal Victoria Hospital, Montreal. In 83 patients satisfactory to excellent analgesia was obtained, and in only 2 patients was no response observed. With 60 mg. administered subcutaneously the onset of action of Nisentil averaged 8 minutes. This action reached its maximal effect in 14 minutes, and showed duration of effect for 1 hour and 43 minutes. The addition of scopolamine delayed the onset of action, with no change in the time of its maximal effect nor its duration. The duration of labour was not affected. Only minimal side reactions were observed, the most prominent being dizziness and nausea. Respiration remained unaffected, blood pressure and pulse rate slightly lowered in a small number of cases.

Seventy-three babies breathed and cried spontaneously immediately after birth, while 14 showed moderate to marked respiratory depression requiring oxygen and mechanical respiratory aid. In each instance this depression occurred when the drug was used in combination with inhalation anaesthesia. Although administered within an hour of delivery in 18 patients, the baby breathed and cried spontaneously in each instance. One foetal death was reported, due to skull fracture following a difficult forceps delivery in the presence of a contracted pelvis.

Otto Schmidt

306. Methylpentynol in Labour.

By G. BOURNE. *Lancet*, **2**, 522–525. Sept. 11, 1954. 4 tables. 19 refs.

The author records his experience in the use of methylpentynol in 100 women in labour. Comparison of results is made with a control series of 100 women in labour (selected by independent observer). The drug was administered in doses of 0·5 g. and later in the series of 1·0 g. given at intervals of not less than 3 hours. The author records a diminution of apprehension with a remarkable ability to relax as a result of the drug. This effect was accompanied by a reduction in the length of labour in many cases. It is to be emphasized that the drug is not an analgesic and hence pethidine or gas and air was given to the patients. No ill effects attributable to the drug were observed in mother or infant either before or after birth. The author concludes that the drug was useful in improving the patient's cooperation during labour in a large proportion of the cases and that it deserves further trial.

H. H. Fouracre Barns

PUERPERIUM

307. Acute Post-Partum Renal Failure (Lower Nephron Nephrosis) with a Report of Two Unusual Cases.

By J. M. JONES. *Med. J. Aust.*, **2**, 179–181. July 31, 1954. 11 refs.

A general discussion of lower nephron nephrosis and the "shunt mechanism" precedes a detailed report of 2 cases.

The first followed post-partum haemorrhage and severe shock and was treated successfully along the lines recommended by Bull, Joekes and Lowe (*Lancet*, 1949, **2**, 229). The second followed intravascular haemolysis of unknown origin.

The author refers to the work of Mason and Mann (*Amer. J. Physiol.*, 1931, **98**, 181) who showed that renal vessels will tolerate a certain amount of free haemoglobin in the blood-stream but when the amount is increased above a certain threshold they respond with contraction.

S. Devenish Meares

308. A Cause of Liver Failure in the Puerperium.

By J. J. SEAVE. *Med. J. Aust.*, **2**, 293–294. Aug. 21, 1954.

A woman aged approximately 30 years was admitted to the Rabaul Native Hospital, New Guinea. Her 3 previous pregnancies had apparently been normal. She was delivered of a stillborn infant weighing 6 pounds

14½ ounces. There had been a history of vomiting during this pregnancy and after a normal delivery she vomited dark fluid several times.

The abdomen was distended and slightly tender and the general condition fair. Anaemia was present. There was an oozing of blood from skin lesions on both legs which resembled yaws lesions. The blood pressure was 85 mm. of mercury systolic and 55 diastolic. She steadily deteriorated and died 4 hours after delivery. Necropsy showed gastro-intestinal haemorrhage, toxic cirrhosis of the liver and toxaemia of pregnancy.

The liver showed granular degeneration, dissolution and fatty infiltration. There was much fibroblastic reaction in the portal tracts and in areas where necrosis of the parenchyma had occurred.

The patient had had one attack of jaundice some years earlier, several recent attacks of malaria and two courses of "Novarsenobillon"; the total dose of one course was 3 g.

The author notes that the main clinical features were the absence of jaundice, the vomiting during pregnancy and the terminal shock. From the commentary it would seem that the author regards nutritional factors as being more important in this case than factors such as arsenotherapy, infective hepatitis and toxaemia of pregnancy.

S. Devenish Meares

309. **Hypopituitarism following Post-Partum Necrosis of the Anterior Pituitary.**

By R. W. Hornabrook and J. E. Caughey. *N.Z. med. J.*, **53**, 210–216. June 1954. 1 table. 9 refs.

From 1938 to 1952 in the Queen Mary Maternity and Dunedin Hospitals, there were 157 deliveries complicated by post-partum haemorrhage (30 ounces or more). Of these 70 women were traced and interviewed, together with 40 control cases. In these 70 cases, 30 had haemorrhage without shock or collapse, 17 had slight or moderate shock, and 23 had severe or prolonged shock. One case only experienced a pronounced change following haemorrhage (with severe shock lasting 2 hours). She had all the features of advanced hypopituitarism. Two other patients showed evidence of mild hypopituitarism and 30 showed minor changes which may indicate a very restricted lesion of the pituitary with resulting impairment of function of a single end organ. It was significant that all the observed cases of clinical hypopituitarism occurred in cases complicated by haemorrhage, but the incidence in this series was not as high as that recorded by previous authors (Sheehan, H. L., and Murdoch, R., *J. Obstet. Gynaec. Brit. Emp.*, 1938, **45**, 456).

L. Woodrow Cox

INFANT

310. **The Remote Effects of Prolonged Labor with Forceps Delivery, Precipitate Labor with Spontaneous Delivery, and Natural Labor with Spontaneous Delivery on the Child.**

By H. B. W. Benaron, M. Brown, B. E. Tucker, V. Wentz and G. K. Yacorzynski. *Amer. J. Obstet. Gynec.*, **66**, 551–566. Sept. 1953. 4 tables. 5 figs. 56 refs.

This study was carried out on a group of 135 children between the ages of 5 and 15 years, born in their own homes, in the Chicago Maternity Centre, and chosen from birth records. The children were divided into 3 groups of approximately equal size, 47 being in the prolonged labour with forceps delivery group (30 high or mid forceps and 17 low forceps); 45 in the precipitate labour with spontaneous delivery group (mostly multiparae) and 43 in the natural labour with spontaneous delivery group. After an operative case was selected for study and the child located, the nearest natural and precipitate labour cases were selected in which the children corresponded in chronological age. As the women were delivered at home no general anaesthetics were used in normal labour and sedatives only in 6 per cent.

In all groups and controls the children were assessed for variations in their physical and mental development by paediatric, neurological and psychological examination and tests. The general conclusions were: (1) if the child survives the neonatal period his chances of growth and development are equal after prolonged labour and forceps delivery and after natural labour with spontaneous delivery; (2) there is no difference in the growth and development of the child who has severe apnoea after long labour and forceps delivery and of the one who breathes spontaneously; (3) precipitate labour and delivery are more deleterious to growth and development than either natural delivery or prolonged labour with forceps delivery. The authors do not consider the results as conclusive as the numbers are too small and the examination and testing limited to one period.

F. J. Browne

311. **The First Ten Minutes.**

By H. B. Atlee. *Canad. med. Ass. J.*, **71**, 227–233. Sept. 1954.

In discussing the problems which arise in the vital first 10 minutes of life the author has outlined his management of the baby, and has emphasized the role played by the obstetrician, who must accept the responsibility for all but a minor fraction of neonatal deaths, the results of complications arising during pregnancy, labour and the immediate neonatal period.

Firstly, the baby should not be allowed out of the hands of the obstetrician until it is breathing properly and has a good pink colour all over its body. To establish a clear airway, the baby is held upside down (a position to which the foetus has become fully accommodated *in utero*) for 5 minutes by the clock, allowing drainage of amniotic fluid. Where this fails to clear the upper respiratory tract, it is better to proceed at once to catheterization of the trachea with a laryngoscope. The author's experience with resuscitating machines has not been a happy one, and he prefers attaching an oxygen bag to the catheter and creating negative and positive pressure with the hand against the bag, where resuscitation is required.

Secondly, the baby should remain attached to the mother until it has received all its blood from the placenta (until the cord has stopped pulsating) the

blood obtained being the equivalent of a transfusion of 1,000 ml. to the average adult. Arguments of hampering the baby's heart by putting too big a load on its circulation, and of an increased tendency to intracranial haemorrhage, have been termed "illogical ratiocinations" by the author.

Thirdly, the newborn baby should be so placed in the delivery room as to be in full view of the obstetrician and nurses. A carriage is described which can be placed against the delivery table under the mother's buttock, with the mother in the lithotomy position and in which the baby lies with its head low. The advantages of such a carriage are that it can be moved quickly if a serious resuscitation problem arises and the baby can be pushed to the nursery with a minimum of handling in the first few hours of life.

Finally, so-called problem babies are discussed, these having been resolved into five common groups, premature, damaged, doped, forceps and Caesarean babies. In addition to the management described, the author has emphasized warmth in a dry towel for the premature baby (abhorring the wet towel), the danger of stimulating the shocked baby as contrasted to the need for constant stimulation of the doped baby, and careful selection of anaesthesia in forceps deliveries and Caesarean sections. The author's results with Nalline have been inconclusive, and he has abandoned the use of alpha lobeline. The need for drainage of the baby delivered by section is re-emphasized, and the author has seen no need for haste in the operation after delivering the baby from the uterus, nor the need for suctioning the stomach.

Otto Schmidt

312. Mount Everest In Utero.

By N. J. EASTMAN. *Amer. J. Obstet. Gynec.*, **67**, 701–711. Apr. 1954.

In this, his Presidential Address to the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Eastman discusses the serious and often fatal effects of hypoxia at high altitudes including Mount Everest, the height of which is 29,141 feet. Yet the normal foetus *in utero* exists in an environment in which the pressure of oxygen corresponds to 33,000 feet and in which a healthy adult could only survive for a few minutes. The foetus adapts itself to the hypoxia by several mechanisms, the most noteworthy being a pronounced increase in haemoglobin. The average concentration of haemoglobin in the blood at birth is 17 g. per 100 ml., a figure 20 per cent higher than that of the average adult or older child. Also the foetal haemoglobin can release oxygen more readily than that of the adult. As a result of these oxygen relationships the foetus exists in a continuous state of cyanosis, yet seems to thrive in it. The meagre oxygen supply is often still further depressed, as during the uterine contractions, placental separation, cord compression, etc., and anoxia is the commonest cause of foetal death and stillbirth.

Cerebral palsy is estimated to occur in 5·9 per 1,000 of infants that survive one month. Of 61 infants with cerebral palsy in the Johns Hopkins Hospital the prenatal records of the mothers showed that there was irregular and repeated vaginal bleeding, both early and late, in a disproportionately high percentage, and 18 (30 per cent) had been born prematurely—3 times the usual incidence of prematurity, while a second stage in excess of 3 hours occurred 6 times more often in the palsy group than in the clinic as a whole. In 33 of the 61 infants the condition at birth was described as poor, thus suggesting intra-uterine damage. Clinical evidence of this damage is usually transitory, for after a few days the infant recovers, and no one suspects that some of his most important cerebral centres are destroyed. It is only when the child reaches the age when it first needs the centres for speech, coordinated locomotion and reasoning—that is, the third or fourth year—that the tragedy becomes manifest.

From 10 to 20 per cent of babies who weigh less than 3½ pounds at birth become blind within the next year as a result of retrolental fibroplasia, which is now regarded as a response of immature neural tissue to anoxia. This anoxia may exist primarily because of inadequate oxygenation of the blood, or it may be induced by exposing a premature infant to an environment of high oxygen concentration and then withdrawing it so rapidly that the physiological changes of acclimatization (increase of haemoglobin, etc.) cannot take place before irreparable harm is done to rapidly developing areas such as the retina. In view of the low oxygen tensions to which an infant is accustomed before birth, it is understandable that oxygen therapy soon after birth at extremely high and vacillating pressures might well have injurious effects.

F. J. Browne

313. The Management of Haemolytic Disease of the Newborn.

By W. WALKER and S. MURRAY. *Brit. med. J.*, **2**, 126–129. July 17, 1954. 3 refs.

The diagnosis of haemolytic disease of the newborn can be predicted before delivery and established within minutes of birth. The authors hold that efficient management will result in a mortality rate of 2 per cent of live-born infants and that the recorded mortality of 14 per cent in England and Wales in 1952 represented a needless loss of 367 infants.

The experience of the Northern Region in 1952–3 is described. The scheme of management was based on the calculation that at least 5 of every 1,000 born will suffer from the disease; 10–15 per cent of these will be stillborn and 60 per cent of the live-born infants will need transfusion. Hospital delivery in the main centre or in 3 outlying hospitals was offered to all mothers with antibodies. Unfortunately, 25 per cent of cases were only diagnosed after delivery. Premature induction of labour was not practised unless indicated for other reason. The usual treatment of the infant was exchange transfusion using 80 ml. per lb. within 9 hours of birth, if the baby had a positive Coombs' test and a haemoglobin level of 14·8 g. per cent or less, or if the level were under 17·7 g. per cent and the bilirubin level greater than 2·7 mg. per 100 ml. These estimations were made on cord blood and the importance of obtaining satisfactory samples is stressed.

Results in 451 cases provide ample evidence that delivery in special centres produces a significantly higher foetal salvage than obtains elsewhere. Thus 7 deaths occurred in 217 infants born in the Newcastle special hospitals and 6 in 38 infants born in other hospitals in the area. Moreover, 4 of the 7 deaths in the Newcastle hospitals, but 16 out of the 17 deaths in the "outside" cases, were the direct result of haemolytic disease.

The authors are reassured by the fact that they were able to predict mild disease not requiring treatment in the expected 40 per cent of live-born infants. None of these infants died from haemolytic disease nor developed sequelae that could be attributed to it.

Recommendations based on their experience are that steps should be taken to achieve 100 per cent prediction of haemolytic disease by antenatal testing and that all mothers with antibodies should be delivered in a special centre which should serve a population of at least 300,000 people. The personnel will only keep in practice if more than 24 cases a year are treated quite apart from the fact that a 24-hour pathological service and provision for ill and perhaps premature infants is difficult to achieve in smaller institutions.

If, for some reason, a mother with antibodies is delivered "outside", a heparinized and a clotted sample of blood should be sent at once to the special centre. There should, however, ideally be no such deliveries outside the centre, for there is no way of predicting the severity of the disease antenatally and cases are quoted showing the extra risk to a severely affected infant if a journey must be undertaken before treatment.

Doreen Daley

314. **Prevention of Kernicterus: Management of Erythroblastosis Foetalis According to Current Knowledge.** By F. H. Allen, jnr. and L. K. Diamond. *J. Amer. med. Ass.*, **155**, 1209–1213. July 31, 1954. 2 figs. 7 refs.

In erythroblastosis foetalis the serious threat to life before birth is anaemia, but after birth jaundice is the important cause of death or of crippling. The metabolism of bilirubin is not fully understood, but the normal newborn infant shows little or no ability to eliminate bilirubin for the first few days of life and this is accentuated in the premature infant. The relation of hyperbilirubinaemia to kernicterus has been proved and it is highly probable that bilirubin in high enough concentration is toxic.

From the Boston Lying-in Hospital the authors record the results of treatment of 193 infants with erythroblastosis foetalis during the 8½ years ending in June, 1953. Towards the end of this period, when the significance of jaundice was fully appreciated, kernicterus was completely eliminated by exchange transfusion. The other factor in the reduction of mortality has been the realization that many of these infants have congestive heart failure with raised venous pressure. The venous pressure is measured frequently during the transfusion by raising the catheter vertically above the abdomen, and an attempt is made to keep the venous pressure at 70 or 80 mm. of blood, if necessary by removing more blood than is given. They have not found any prenatal treatment, including the administration of steroid hormones, to be of value.

Exchange transfusion is generally indicated in the following circumstances: (1) When there is clinical evidence of the disease at birth, (2) a history of kernicterus in a previous baby, (3) a haemoglobin of less than 15 g. per cent, (4) prematurity, (5) a maternal titre of antibody higher than 1:64, (6) if jaundice becomes apparent before the infant is 6 hours old, and (7) if the serum bilirubin reaches 10 mg. per 100 ml. in the first 12 hours. A high or rapidly rising bilirubin level after the initial transfusion is now regarded as an indication to repeat the exchange transfusion.

D. W. James

315. **Cerebro-meningeal Haemorrhages of the Newborn.** (Le emorrhagie cerebro-meningee del neonato con particolare riguardo alla diagnosi precoce a alla terapia.) By M. Uglietti. *Minerva ginec., Torino*, **6**, 601–614. Sept. 15, 1954. 49 refs.

Statistics of different authorities on the frequency of this complication of delivery show wide variations according to the proportion of abnormal labours, premature babies and stillbirths included in the totals considered. Obviously, difficult labours including prolonged labour, excessive moulding, and forceps cases supply many examples, but a relatively easy labour also carries a much increased risk for a premature infant. The figures reviewed show 3·1 per cent among "prems" as against 0·85 per cent at term. Even Caesarean sections provide a quota, more especially where the head has been levered out with some force, and the advent of the antibiotics has resulted in abdominal delivery being carried out in numerous cases where the child has already been subjected to severe and prolonged uterine contractions. Whilst dystocia is the prime causative element, the two main contributing factors are prematurity and asphyxia. The importance of a foetal intrinsic factor such as a deficiency of vasculo-protective substances, vitamins E or K, or some allied blood condition, is probably not marked, but in prematures there is a notable fragility of the vessels as can be shown by comparing the result of simple suction to the skin of premature and full-time infants.

As for asphyxia, it is arguable that this is the result and not the cause of the haemorrhages, which in this case are of the widespread capillary type rather than gross haemorrhage due to rupture of large vessels.

Clinical signs. Leaving aside such controversial matters as the relation of clinical signs to the type and situation of the haemorrhages, or even as to whether such signs do indicate that haemorrhage has occurred, the clinical signs to be considered must be looked for within the first few hours of life if useful action is to be taken. There are the characteristic cries and complaints of the infants, readily recognized by experienced midwives, shallow breathing, paleness or blueness of the extremities, lowered temperature, jerky movements of the limbs especially when the child is disturbed, and the characteristic "boxer's attitude" with head retracted and fists clenched. Other signs may be unexplained diarrhoea and

loss of weight. Severe asphyxia is usually associated with petechial haemorrhages in the brain substance and in prematures this may be accompanied by bleeding into the ventricles. Meningeal haemorrhages can be extradural (tentorial and falx tears), subdural (more common) or subarachnoid, or a combination of these.

Positive diagnosis can be made by various types of puncture, but for practical purposes ordinary spinal puncture is both diagnostic and therapeutic. It is also devoid of risk even to the frailest child. The C.S.F. may be (1) yellowish with moderate hypercytosis, the non-pathological pre-icteric type, (2) clearly bloodstained but non-coagulating, with a marked hypercytosis, or (3) heavily bloodstained so as to resemble almost undiluted blood. The C.S.F. is also under increased pressure in both (2) and (3).

The withdrawal of up to 10 ml. of the C.S.F. if bloodstained or under increased pressure is advised and this can be repeated every 2 or 3 days till adequate improvement is obtained in its colour and cytology. A table of 36 such cases so treated is given and the results are claimed fully to justify the procedure.

W. C. Spackman

MATERNAL MORTALITY

316. **Medico-legal Aspects of Unexpected Death in Labour.** (Aspetti medico-legali della morte improvvisa in travaglio di parto.)

By F. TARSITANO. *Minerva ginec., Torino*, **6**, 75–79. June 30, 1954.

Excluding deaths clearly due to violence or to such patent causes as placenta praevia or serious heart disease, some cases of death in labour may lead to accusations of negligence or worse being made against the attendant at the confinement, whether doctor or midwife. As examples, the attendant gives a perfectly usual and routine injection or even makes an internal examination to a semi-hysterical patient who shortly afterwards collapses or develops fits and dies due to some pre-existing pathological condition such as a severe toxaemia; or towards the end of a difficult labour in a debilitated woman the very commencement of general anaesthesia produces a fatal syncope. Short of an actual accusation of malpraxis, a campaign of innuendo may be instituted against the unfortunate attendant with disastrous results.

The author gives a list of 24 such cases within his experience as teacher of forensic medicine, and after analyzing each comes to the conclusion that in none of them was there any real justification for attempts that were made to fix culpable responsibility on the attendant.

W. C. Spackman

OBSTETRIC OPERATIONS

317. **Uterine Closure in Caesarean Section.**

By M. POTTER. *Amer. J. Obstet. Gynec.*, **67**, 760–765. Apr. 1954. 7 figs. 4 refs.

The author uses interrupted silk sutures in both classical and lower segment Caesarean sections. Since 1941 he has performed 1,521 Caesarean operations without any maternal mortality or scar rupture. In the classical operation the sutures enter 1 cm. from the incision and pass through the myometrium at a depth approximately one-third of the thickness of the uterine wall, and are placed about 2 cm. apart. The knots should be kept to one side of the incision, should be cut close and should be tied tight enough to maintain co-aptation of the muscle without blanching it. For the lower segment operation the method is the same except that a bladder flap is freed and, in closing, the interrupted sutures are placed to a depth of half the thickness of the myometrium. The bladder flap is closed over the silk sutures, using plain fine catgut.

It is claimed that unlike continuous suturing this technique causes little or no ischaemic necrosis; as little suture material is used there is little or no suture reaction.

F. J. Browne

318. **Vaginal Delivery Following Caesarean Section.**

By L. P. BENGTSSON. *Acta obstet. gynec. scand.*, **33**, 318–326. 1954. 13 figs. 5 refs.

During the 40-year period 1910 to 1949 there were 1,297 Caesarean sections and 214 vaginal deliveries following Caesarean section at the Obstetric Clinics of Lund and Malmö (Sweden). Only 133 of the latter cases, in which the vaginal deliveries (producing 138 infants) were the first ones following the sections, were included in the present investigation; 84 of these were "obstetrical primiparae", i.e., the section had been done to terminate a first pregnancy, and 49 were "obstetrical multiparae", i.e., there had been one or several vaginal deliveries and/or miscarriages before the section. The average ages of obstetrical primiparae and multiparae were 28·4 and 35 respectively. In about two thirds of the mothers under review vaginal delivery took place within 4 years of the section. The commonest indications for the sections preceding vaginal deliveries were placenta praevia, abruptio placentae and toxaemia, but there were no fewer than 30 cases in which the section was indicated by cephalo-pelvic disproportion. The type of section was corporeal 18 times, cervico-corporeal 93 times, and low transverse and unknown 11 times each.

No instance of maternal death or of rupture of the uterus occurred in the 133 cases studied. The duration of labour was no longer in obstetric primiparae following section than in ordinary primiparae of the same age. The incidence of obstetric operations, including artificial rupture of the membranes, episiotomy and manual removal of the placenta, was 25·6 per cent, i.e., between the incidence of similar operations in ordinary primiparae and in all deliveries at the same hospitals; the incidence of forceps deliveries was 11·3 per cent. Puerperal complications (pyrexia, haemorrhage, thrombophlebitis) occurred 13 times (10 per cent). The infantile morbidity was 3 per cent, half of which were slight birth-injuries. The perinatal loss was 21, i.e., 15·2 per cent. Eight foetuses died *in utero* before the onset of labour, and 13 were lost during or after labour (10 from asphyxia, and 1 each from intracranial haemorrhage, prematurity and anencephaly). It is concluded that this

high perinatal loss could have been reduced by performing elective repeat Caesarean section in some of the 30 cases in which the original section had been indicated by cephalopelvic disproportion. *N. Alders*

GYNAECOLOGY

319. **Effect of Thyroid Therapy on Menstrual Disorders and Sterility.**

By C. L. BUXTON and W. L. HERRMANN. *J. Amer. med. Ass.*, **155**, 1035–1039. July 17, 1954. 5 figs. (22 refs. In authors' reprints only.)

Although the occurrence of menstrual abnormalities in thyroid disorders is well known, the relationship of the thyroid gland to the complicated pituitary-gonadal-endometrial axis is not clearly understood. From the Sloane Endocrine and Sterility Clinic, New York, the authors have investigated the prevalent view that thyroid extract is of value in the treatment of sterility and menstrual disorders in the euthyroid patient.

Patients were divided into two groups. In Group A 195 euthyroid patients with complaints of sterility, amenorrhoea, oligomenorrhoea, and menometrorrhagia without apparent cause, were given only one grain (60 mg.) of thyroid extract daily, and this dose was varied according to tolerance. In Group B 144 similar patients were given placebo tablets in place of the thyroid. Laboratory control was carried out by determinations of basal metabolic rate, protein-bound iodine, radioactive iodine uptake, and serum cholesterol levels. There was no possible correlation between the laboratory tests in any one patient and it was concluded that unless a patient had clinical signs of hyperthyroidism or hypothyroidism the available laboratory tests of thyroid function were not of great diagnostic value, and in some cases were even misleading.

For various reasons it was only possible to follow up 75 patients in Group A and 56 patients in Group B, and the differences in cure and improvement rates between the two groups were not statistically significant. It appeared that the administration of exogenous thyroid merely replaced the endogenous thyroxine that the thyroid gland ordinarily would be producing were it not permitted to rest because of this "outside assistance" in maintaining its function. The authors conclude that the therapeutic value of thyroid administration for the conditions described is very questionable.

D. W. James

320. **Studies in Hirsutism. I. Urinary Excretion of the Neutral 17-Ketosteroids.**

By J. W. JAILER and R. L. VANDE WEILE. *Gynaecologia, Basel*, **138**, 276–287. Aug. 1954. 4 figs. 36 refs.

A study has been made of a series of 78 women referred to an endocrine clinic on account of hirsutism.

The excretion of neutral 17-ketosteroids in normal women has been found to be between 6 and 15 mg. a day.

In 17 of the 78 hirsute women, excretion of 17-ketosteroids was found to be raised to a range of between 15 and 35 mg. a day. Most of these had normal menstrual cycles and some of them had had no difficulty in becoming pregnant in the past. Presacral aerograms in 8 of these patients showed no evidence of adrenal tumour. Administration of cortisone to women with congenital adrenal hyperplasia has been found to cause a fall in 17-ketosteroid excretion to normal levels, with a decrease in other steroids also.

In 27 of the group of 78 patients with hirsutism evidence was found of polycystic ovaries with a normal excretion of 17-ketosteroids. Wedge resection of the ovaries was followed in 85 per cent of cases by the resumption of more or less normal menstrual cycles.

In the remaining 34 patients menstruation and excretion of 17-ketosteroids were normal. These are described as "constitutional" or "idiopathic" hirsutism.

[The symptom of hirsutism in women is one of the most distressing and difficult problems of female endocrinology. This work helps in classifying these cases. It seems a pity that the author does not indicate whether treatment with cortisone or wedge resection of polycystic ovaries had any effect on the hirsutism itself.]

Josephine Barnes

321. **Endometriosis and Sterility.**

By R. MACKEY. *Med. J. Aust.*, **2**, 168–169. July 31, 1954. 2 refs.

The paper deals solely with endometriosis amongst those patients attending the sterility clinic at The Women's Hospital (Crown Street) and those from the private practices of the author and Alan M. Grant.

Amongst the Clinic cases the known and absolute percentage incidence was 0·6. The average age was 28 years. The average duration of sterility was 2·5 years. In all cases conservative surgery was performed, cysts being removed or resected and areas of endometriosis excised and in all cases the uterus was ventro-suspended.

Of the patients treated 46·6 per cent became pregnant. The author considers that operation offers the best chance for pregnancy. Evidence of tubal damage provided by Rubin's test or salpingography may be confirmatory though normal test results do not exclude it.

Pelvic tuberculosis must be excluded by endometrial biopsy and culture prior to surgery being undertaken. Culdoscopy will aid diagnosis in the early cases.

S. Devenish Meares

322. **A Study Concerning the Ascent of Spermatozoa in the Female Genital Tract.** (Étude à propos de l'ascension des spermatozoides dans les voies génitales de la femme.)

By J. SEGUY and J. VIMEUX. *Gynéc. Obstét.*, **53**, 144–153. 1954. 10 figs. 4 refs.

In the course of a series of experiments with human and rat spermatozoa, the writers attempted to define the functions of the barriers encountered in the genital tract of the female, in particular those conditions which might interfere with the direct progress of sperms towards the ovum.

The meeting of sperm and ovum did not appear to them to be the result of a specific tropism. Spermatozoa animated by rectilinear movement, invariably move forwards and take up their position only in such media as are

sufficiently favourable to them. Certain obstacles encountered in their path cause concentrations of sperms and give the illusion of their being attracted together there.

D. Maxwell

323. **Histological Investigations (Testicular Biopsy) in Aspermic-Azoöspermic Patients and Their Treatment.** (Über histologische Befunde (Hodenbiopsie) bei Aspermien-Azoospermien und deren Behandlung.)

By R. WEYENETH. *Arch. Gynäk.*, **184**, 420–458. May 1954. 15 figs. 2 tables. 36 refs.

Aspermia, i.e., absence of mature spermatozoa as well as of all germinative cells in the ejaculate, is subdivided into 3 groups: (1) mechanical aspermia, (2) functional aspermia (dysfunction of adnexa) and (3) true aspermia.

(1) Mechanical aspermia is due to bilateral occlusion or congenital absence of the vasa deferentia with normal testicular histology.

(2) Functional aspermia comprises patients capable of producing normal masturbation specimens, with sterile ejaculates at intercourse. Histological findings in such cases show no abnormality and the disturbance appears to be psychogenic.

(3) True azoö-aspermia due to faulty spermatogenesis is either, (*a*) a congenital developmental disturbance or (*b*) an acquired lesion, the former comprising about 20 per cent of all cases of male sterility. From the histologist's point of view these cases are clearly of great interest and the author discusses them in detail.

Congenital aspermia and developmental arrest show a definite histological pattern which varies in severity according to the degree of the lesion. There is a maturation failure of the seminiferous tubules, an absolute or relative increase of Leydig cells, a normal membrana basalis but often a thickening of the membrana propria and frequently also peritubular fibrosis.

The author subdivides this group into 3 aetiological subgroups, viz., idiopathic, endocrine and traumatic. The *idiopathic* group comprises 3 separate entities: (1) germinal aplasia (aspermia, normal adnexal development, small testicles, increased F.S.H. excretion and preservation of sexual potency); (2) primary gonadal lesion with associated endocrine disturbances; (3) progressive fibrosis of the seminiferous tubules producing the Klinefelter, Reifenstein and Albright syndrome of gynaecomastia, small testicles, aspermia and reduction of spermatogenesis following progressive occlusion of seminiferous tubules, increased F.S.H. and decreased 17-ketosteroid excretion.

The secondary aspermias, on an *endocrine* basis, are subdivided into (1) hypogonadotrophic eunuchoidism (testicular underdevelopment, absence of gynaecomastia, diminished gonadotrophin- and 17-ketosteroid excretion, absence of secondary sexual characteristics and arrested spermatogenesis with maturation failure of Leydig cells) and (2) undescended testicles.

The *traumatic* group is a questionable entity ascribed to secondary haemorrhage following breech delivery. The haematomata are alleged to cause atrophy and fibrosis of the seminiferous tubules, thus provoking early castration.

Acquired azoö-aspermia (postpuberal) is due to a variety of causes such as endocrine factors, circulatory disturbances, general nutritional causes, toxins and infections (mumps, pneumonia, typhoid, septic throat infections, high doses of sulphonamides) mechanical damage, chronic diseases, e.g., diabetes and nephritis, and administration of high doses of oestrogens and androgens. These patients have a normal appearance, normal 17-ketosteroid and gonadotrophin excretion values, whereas testicular biopsies show varying degrees of atrophy.

In contrast to the histological classification of azoöspermia, there is the clinical classification as suggested by Nelson and Heller which may prove more practical. This is based on symptomatology, age at onset and primary site of lesion. The patients fall into 2 main groups: those complaining of sterility plus symptoms referable to diminished androgen production, and those whose sole complaint is sterility. The first group, under the heading of eunuchoidism, is subdivided into hypergonadotrophic eunuchoidism (Klinefelter, Reifenstein and Albright's syndrome, Heller, Nelson and Roth's syndrome and Heller and Nelson's syndrome of "Sertoli cells only") and hypogonadotrophic eunuchoidism following a pituitary/diencephalic lesion.

The second group of patients complaining of sterility only in the absence of endocrine disturbances is subdivided into (1) mechanical aspermia due to occlusion or absence of the vasa deferentia, (2) germinal aplasia, (3) maturation failure and (4) generalized peritubular fibrosis.

The treatment of "mechanical aspermias" is surgical (vaso-epididymostomy). Hypogonadotrophic eunuchoidism usually responds to treatment with gonadotrophins. No cure is known for primary testicular lesions and only substitution therapy with testosterone has any effect.

E. Wachtel

324. **Betatherapy in Pelvic Inflammations.** (Betaterapia nelle flogosi genitalia.)

By A. NARPOZZI. *Riv. Ostet. Ginec. prat.*, **36**, 194–197. Apr. 1954. 17 refs.

The author used ovules containing minute doses of radioisotopes emitting Beta rays, approximately 361 millimicrocuries per ovule, in 20 patients with subacute inflammation of the uterus and appendages, and in 20 patients with chronic cervicitis.

In the first group 1–2 vaginal ovules were given daily for 15–20 days. By the end of this time all the patients were free of symptoms; the temperatures, white blood cell counts and sedimentation rates were normal; and tubo-ovarian masses had decreased in size and, in some instances, had disappeared.

In the second group 1 vaginal ovule was used nightly for a fortnight. When the course was finished almost all the women were cured. Cauterization was necessary in only a few of them.

M. Caturani

325. **Prophylaxis and Early Diagnosis of Uterine Cancer.** (Profilassi e diagnosi precoce del cancro dell'utero.)

Minerva ginec., Torino, **6**, 313–352. May 15, 1954.

This number is largely taken up with papers read at the 44th Congress of the Italian Obstetrical and Gynaecological Society on the above subject.

George Papanicolaou of Cornell presents a long article on the cytological diagnosis of uterine cancer, well illustrated by 22 plates. Hans Hinselmann of Hamburg gives his experiences from combining televising with his colposcope, and with a similar method of televising microslides (10 plates). In spite of good definition and easy vision at big magnifications the absence of colour in televised colposcopic views limits its effectiveness.

Professor Rochat of Lausanne talks on amputation of the cervix in treating intra-epithelial cancers of the cervix. He rightly begins by stating that such a procedure must appear dangerously conservative even when limited to what is variously known as non-invasive or pre-invasive cancer, epithelioma-in-situ or cancer in stage O. The three best known methods of diagnosing non-invasive cancer are by Schiller's glycogen test, by colposcopy and by cervico-vaginal cytology, the principal protagonists of the latter two methods being Hinselmann and Papanicolaou respectively. These methods depend on changes in the epithelial cells and not on their invasive situation. In cases where such "atypical" cells are found loose in the vagina or cervix without a local subepithelial invasion it is to be presumed that invasive cancer will sooner or later make its appearance. On the other hand, the histopathologist does not make a diagnosis of cancer till an "anarchic" penetration of the basal layer can be demonstrated in microsections.

It is agreed that a definite positive diagnosis of cancer can only be made by histopathology and that such cases call for full radical treatment. But what of the cases showing an atypical cytology without invasive change? It is with such cases that Professor Rochat deals. He considers that such cases can be treated simply by amputation of the cervix, and he quotes a series of 30 cases so treated. Briefly, having obtained a positive cytological test, he does two separate curettages, the first of the cervix and later one of the corpus, to exclude an invasive cancer in either situation. Moreover, after amputation, the cervix is submitted to serial sectioning to confirm that no invasive form is present. In this series, no further evidence of atypical cells has been found in any case on repeated cytological examination. The length of follow-up is, however, too short to be conclusive, the method being a recent one (since 1950).

Professor Dellepiane's paper is statistical for cancer in general and genital cancer in particular, stressing the well-recognized fact that the best results of treatment are in the earliest cases, and that the aim must be to get it in the pre-invasive phase if possible.

Carlo Mossetti deals with the methods used in examining women for early cancer in Dellepiane's clinic, the colposcopic appearances, the tendency for slight trauma, including deliberate squeezing of the cervix, to produce bleeding, Schiller's test (given in full detail) and the cytological tests. He stresses that none of these tests is infallible nor devoid of difficulties and drawbacks, and it is remarked that a very extensive series of tests has to be made at great labour to find in the end a very few positive or doubtful cases. However, the actual cost in money and labour of diagnosing one early case is much less than that incurred in looking after one incurable patient; in addition a patient's life is probably saved. In N. America, reliance is placed on speculum examination, cytology, and annular biopsy, whilst in Europe and S. America the speculum, colposcope and biopsy are used. Statistics are quoted which show extremely wide variations in the number of cancer cases spotted among general obstetrical and gynaecological patients, but apparently about 1·5 per cent of unhealthy cervices (lacerations, erosions) show cancer by one test or another. The cervix is first swabbed with 4 per cent acetic acid to remove mucus and can then be treated with Lugol's Iodine for the Schiller test. A light scraping with a small spoon or curette is to be used if only a superficial biopsy of epithelial cells is to be taken, and a ring or looped diathermy terminal is useful for a deeper biopsy from inside the cervical canal. All these tests can be done without hospitalizing the patient. The paper is illustrated with some good plates of non-invasive cancer.

L. Cusmano and P. Feletig submit papers on the study of the nuclei of abnormal cells in the cytological diagnosis of cancer. The nuclei are stained by special methods after the cellular cytoplasm has been dissolved in acetic alcohol for upwards of 24 hours (10 plates).

Luigi Bacialli describes a colpomicroscope giving a direct view of the cervix at a magnification of 160 to 200 diameters. Hinselmann's colposcope gives 16 to 20 diameters.

It appears on considering the whole discussion that not only are the methods very laborious but that the interpretation of the individual tests is at present a matter calling for very experienced judgment and is not seldom equivocal in the early pre-invasive phases of the disease. The personal factor makes the results of one observer differ materially from those of another. There are many sources of error and divergence of opinion is easy. Biopsy can miss the affected tissue, but can at least give a definite positive or negative for the portion studied. Unfortunately its successes are so much more usual in the invasive than in the pre-invasive phase.

As regards prophylaxis, it is stated that in some countries life insurance companies require and pay for an annual medical overhaul, but would the women agree and even so would this really help to spot the early cases of uterine cancer? Education via the popular women's magazines (which are nowadays so much more outspoken than formerly) appears the best line, so that the earliest symptoms needing medical investigation can be recognized, and the curability at this stage realized.

W. C. Spackman

326. **Carcinoma of the Corpus. Its Classification and Treatment.**

By H.-L. KOTTMEIER. *Gynaecologia, Basel,* **138,** 287–310. Aug. 1954. 47 refs.

This is an important review embodying work carried out at the Radiumhemmet, Stockholm between 1936 and 1948.

The classification is based on that used in the Stockholm Annual Report and is as follows:

Stage I. The growth is confined to the uterus

Group (1): Operation advised.

Group (2): Bad operative risk.

Stage II. The growth has spread outside the uterus.

Stage O, not discussed in the paper, refers to irregular, atypical endometrial hyperplasia.

In 79·6 per cent of patients symptoms of carcinoma of the corpus started in the post-climacteric period. The menopause is often delayed in these patients. Pregnancy had never occurred in 35·9 per cent. Uterine fibroids were found in 37·7 per cent.

Detailed statistics are given of the results of treatment. In 1,522 patients suffering from carcinoma corporis and carcinoma corporis et endocervicis the absolute 5-year recovery rate was 57 per cent. The author claims that primary radiotherapy adequately administered is just as justifiable as primary surgery in the treatment of corpus cancer.

No correlation was found between the histological type of growth and the cure rate.

In an attempt to study the lymphatic spread of cancer of the corpus, radioactive gold was injected under the endometrium of the fundus uteri in 3 cases. Lymph node dissection was performed 5 to 7 days later. In one case 29 per cent of the injected gold was recovered from the hypogastric lymph nodes. In another, gold was demonstrated only in the iliac glands.

Primary radiotherapy is to be preferred to surgery in patients who are great operative risks.

Josephine Barnes

327. **Choriocarcinoma of the Uterus. Study of 74 Cases from the Mathieu Chorionepithelioma Registry.**

By E. NOVAK and C. S. SEAH. *Amer. J. Obstet. Gynec.,* **67,** 933–957. May 1954. 12 refs. 9 tables. 19 figs.

Two patients in whom pulmonary metastases had been diagnosed by X-ray are alive, 1 for 11 months and the other 4 months after hysterectomy—too short a time to justify their being regarded as cured. In 7 cases the primary uterine tumour disappeared but all died from extensive metastases. Of the 74 cases 11 (14·5 per cent) have remained well for 2 years and 2 others for 1 year since hysterectomy. No hormone studies are reported.

F. J. Browne

328. **Vaginal Cytodiagnosis by the Contrast Phase Method.** (Considerazioni cliniche sulla citodiagnosi vaginale a mezzo del contrasto di fase.)

By A. DE PALO. *Minerva ginec., Torino,* **6,** 534–548. Aug. 15, 1954. 15 figs. 96 refs.

Continuing the search for an easy and rapid method of diagnosing early carcinoma of the cervix, the author describes a method of cytological examination of vaginal smears without the necessity of fixing and staining the slides. The fresh secretions are examined by dark ground illumination and polarized light, the "contrast phase" method. A second method is by intra-vital staining with very dilute solutions of neutral red or Janus green, using at the same time the contrast phase microscope.

Typical photomicrographs of slides from a variety of clinical conditions affecting the cervix are shown. The author claims that the results are obtained more quickly and avoid the fallacies and artefacts sometimes produced by ordinary fixation and staining methods.

W. C. Spackman

329. **Brenner's Tumour.** (Considerazioni anatomico-cliniche e istogenetiche sui tumori di Brenner.)

By E. FERRARIO. *Minerva ginec., Torino,* **6,** 407–423. June 15, 1954. 30 figs. 72 refs.

The author describes in great detail the clinical history and histopathology of a case of Brenner's tumour, and discusses at length its embryological origins (which he traces to Walthard's bodies) and the problem of the origin of the pseudomucinous substance in the intra-epithelial cysts.

As this tumour does not give rise to symptoms till quite large, it is often only discovered accidentally in the course of operations for other conditions. Its frequency, as reported by different authors, varies greatly suggesting that its essential characteristics are not quite agreed upon. It is a solid tumour of mixed fibrous and epithelial elements, usually unilateral and occurring in women of about or after menopausal age.

The author's conclusions are that Brenner's tumour is a fibro-epithelial new growth, usually non-malignant and unilateral, arising from undifferentiated sexual cells of the ovarian cortex or adjacent primitive structures as the result of some stimulus as yet unknown. It is to all intents and purposes undiagnosable before operation and is usually associated with metrorrhagia and endometrial hyperplasia, suggesting that the tumour exercises some hormonal influence.

W. C. Spackman

OPERATIONS

330. **Ureteral Injuries.**

By H. C. FALK and I. A. BUNKIN. *Obstet. Gynec.,* **4,** 4–20. July 1954. 16 figs. 2 tables. 26 refs.

The prevention and management of ureteral injuries occurring during gynaecological surgery for benign disease are separately surveyed in this article. At Beth Israel Hospital, New York, there were 5 recognized ureteral injuries in 6,309 operations. The anatomy of the ureter is distinctly discussed and illustrated with possible anomalies, and the displacements that may occur as a result of tumours, exudates, previous operations, malignant infiltrations or endometriosis. When there is any question of the possibility of injuring the ureter, the best procedure is to expose it throughout its course, without freeing it from the peritoneum.

Pre-operative ureteral catheterization is not routinely performed by the authors who discuss its relative merits. The various procedures to be adopted when injury is recognized at operation are reviewed. The ureter may be ligatured, crushed or completely or partially severed. It may be repaired, transplanted into the bladder or a uretero-ureteral anastomosis may be performed: the results of the latter procedure are frequently not good. If these methods are not possible, it may be transplanted into the sigmoid colon. Simple ligation of the cut ureter is not recommended. The recognition and treatment of injuries after completion of the operation are discussed.

[This is an excellent review of the subject of ureteral injuries, beautifully illustrated.] *J. G. Dumoulin*

331. **Late Urinary System Complications Following Radical Hysterectomy for Carcinoma of the Cervix.**

By W. N. THORNTON. *Amer. J. Obstet. Gynec.*, **67**, 867–879. Apr. 1954. 8 tables. 10 figs. 12 refs.

This study concerns 33 women treated by radical surgery since April, 1948; 12 of them had also received pre-operative X-ray therapy and 4 had radium and X-rays; 28 of the patients were available for follow-up. Of these 28, 6 have developed upper urinary tract complications; in 3 there is a non-functioning kidney, 1 has a non-functioning kidney and hydronephrosis; 1 has unilateral and 1 bilateral hydronephrosis. Two of the most troublesome late developments were urinary incontinence and loss of bladder sensation due to neurological injury, and in some cases the damage seemed to be permanent. The upper urinary tract complications may be encountered many months after operation and are usually silent developments. When they occur in absence of irradiation therapy they seem to be secondary to ureteral stricture of intrinsic origin, or due to fibrosis of the retroperitoneal tissues, involving the ureter. Urological studies are necessary in the follow-up of these patients to detect these complications and to institute treatment before the development of renal complications. *F. J. Browne*

332. **Pelvic Evisceration for Cancer.**

By J. TURCOT, G. ST. ARNAUD and L. COULONVAL. *Canad. med. Ass. J.*, **71**, 1–3. July 1954. 30 refs.

Construction of a substitute bladder after pelvic evisceration is described in a review of 5 cases of carcinoma of the cervix treated by pelvic exenteration after irradiation therapy had proved ineffective. This procedure was performed to avoid infection of the urinary tract by the infected colon, and the psychological trauma following a wet colostomy. In 4 cases the last loop of the ileum, in the fifth the caecum, was utilized to construct this bladder, the technique being described in brief. *Otto Schmidt*

333. **Total and Anterior Pelvic Exenteration. I. Report and Results Based upon 315 Operations.**

By A. BRUNSCHWIG and W. DANIEL. *Surg. Gynec., Obstet.*, **99**, 324–330. Sept. 1954. 8 figs. 3 refs.

It is now more than 7 years since the first total pelvic exenteration was performed, and since approximately 100 total and anterior exenterations were performed more than 5 years ago in the Memorial Centre for Cancer and Allied Diseases in New York, a report is given of the results to date.

The authors describe briefly the extent of total and anterior pelvic exenteration and point out that the objectives envisaged in the earlier periods were merely palliative. Surgery was undertaken because re-radiation so rarely afforded even temporary relief after initial radiation failure.

In all, 315 operations have been performed to 31st December, 1953, 202 total pelvic exenterations and 113 anterior pelvic exenterations. Eighty-four or 26·6 per cent of the patients did not leave the hospital alive. The main causes of death were shock, uraemia, intestinal fistulae, peritonitis and general sepsis. The average blood transfused in all patients was 3,500 ml.

The 5-year cure rate is 12 per cent among 104 patients. The incidence of survival in the 89 patients operated upon during 1950 and 1951 is 30 per cent, i.e., approximately 2–4 year survivors. It should be noted that this is a greater salvage than is possible in advanced cancer of the lung, stomach, pancreas, oesophagus or gall-bladder, achievable by surgery.

Palliation still remains an important objective of the procedure but its evaluation is difficult to define. Certainly survival for 3 years without evidence of disease represents palliation and this was achieved in 28 per cent of the patients operated upon in the period from 1950–1951. The authors, however, believe that even several months' respite from the symptoms presenting before operation also constitutes palliation, and this was achieved in a higher incidence than the statistics given indicate.

From these results it is apparent that pelvic exenteration for advanced pelvic cancer offers effective palliation and also 5-year "cures" when no other known method of treatment can afford opportunity for comparable relief.

John P. Erskine

334. **Super-Radical Surgery. A Problem in Medical Morality.**

West. J. Surg. Obstet. Gynec., **62**, viii–x. Aug. 1954.

This editorial comments favourably on a recent paper (*J. Amer. med. Ass.*, **151**, 711–716, 1953) and gives a clear account of the problems underlying grossly mutilating operations. The conditions reached are that patients should be offered the chance of undergoing these procedures if the surgeon conscientiously believes that the technique can offer the patient something and the fact that the procedure is mutilating does not in itself affect this conclusion. If the surgeon does not think such an operation does offer a reasonable probability of benefit, he is not obliged to inform the patient that these techniques are available.

D. C. A. Bevis

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Each sentence should have its proper components thus:

"*Progress:* The patient continued to improve," NOT

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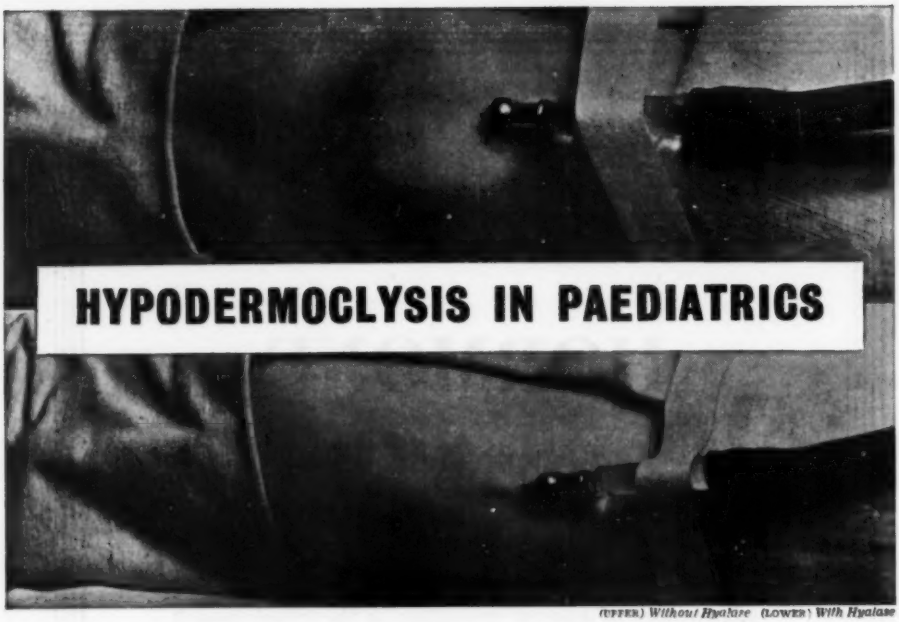

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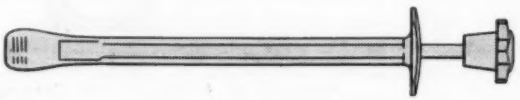

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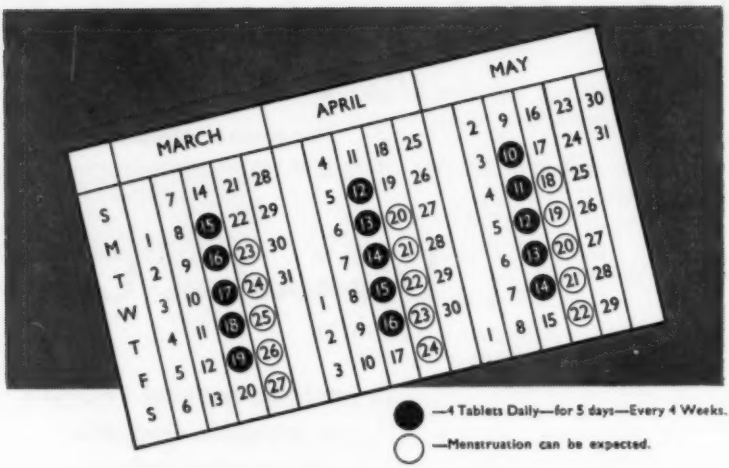

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†Finnerty, F.A., Jnr., and Fuchs, G. J.: Washington, D.C., to be published.

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1. ACTA OBST. GYNEC. SCAND. 1950. 30. suppl. 6.

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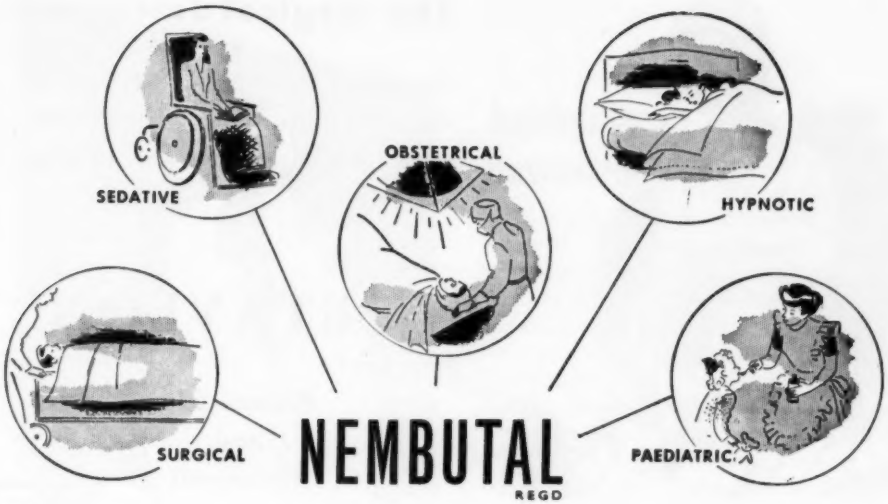

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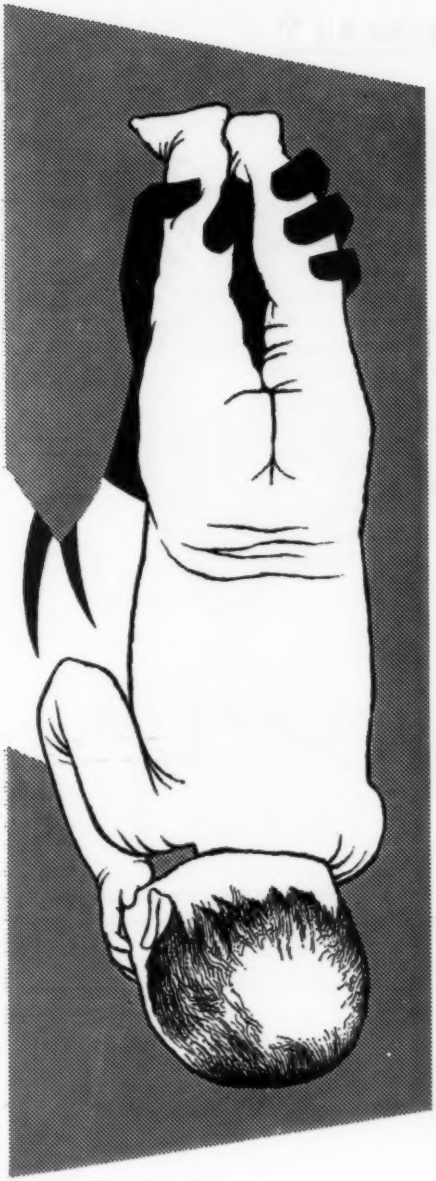

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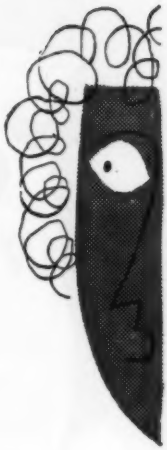

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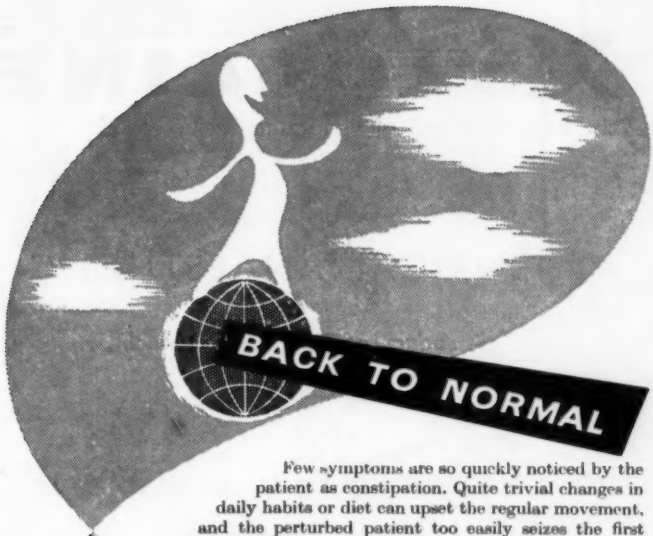

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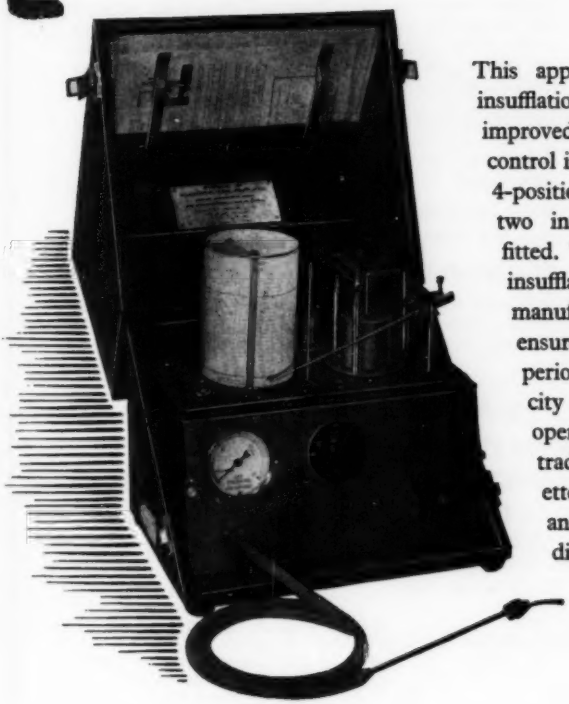

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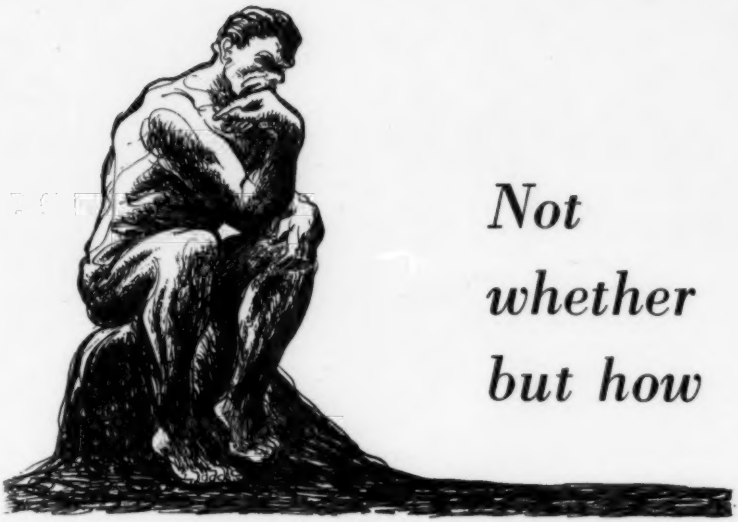

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